

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**203100Orig1s000**

**OTHER REVIEW(S)**

## PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for *each* PMR/PMC in the Action Package.

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NDA/BLA # 203100  
Product Name: Stribild (fixed-dose combination tablet of elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate) 150/150/200/300 mg

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PMR/PMC Description: **1919-1:** Conduct a pediatric pharmacokinetic, safety, and antiviral activity trial of Stribild with activity based on the results of HIV-1 RNA virologic response and safety monitoring over at least 48 weeks of dosing in pediatric subjects from 12 to <18 years of age. Include in the trial safety monitoring assessment of potential renal toxicity (to include serial assessments of serum creatinine, serum phosphate, urine glucose, urine protein, calculated creatinine clearance, glomerular filtration rate (GFR) by cystatin C, and calculated fractional excretion of phosphate) and effects on bone (to include serial DEXA assessment).

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PMR/PMC Schedule Milestones:	Final Protocol Submission:	<u>09/2012</u>
	Trial Completion:	<u>03/2016</u>
	Final Report Submission:	<u>11/2016</u>
	Other:	_____

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

Adult trials are completed and ready for approval.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

The goal of this trial is to provide PK, safety, and anti-viral activity data in pediatric subjects ages 12 to < 18.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

*If not a PMR, skip to 4.*

– **Which regulation?**

- Accelerated Approval (subpart H/E)  
 Animal Efficacy Rule  
 Pediatric Research Equity Act  
 FDAAA required safety study/clinical trial

– **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?  
 Assess signals of serious risk related to the use of the drug?  
 Identify an unexpected serious risk when available data indicate the potential for a serious risk?

– **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?  
*Do not select the above study/clinical trial type if:* such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?  
*Do not select the above study/clinical trial type if:* the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?  
*Do not select the above study type if:* a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

A nonrandomized, open-label, multicenter, two-part, single-arm trial of the pharmacokinetics, safety, tolerability, and antiretroviral activity of STRIBILD (adult formulation) in HIV-1 infected, antiretroviral treatment naïve and/or experienced adolescents 12 to < 18 years of age

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
  - Pharmacokinetic studies or clinical trials
  - Drug interaction or bioavailability studies or clinical trials
  - Dosing trials
  - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
- 
- Meta-analysis or pooled analysis of previous studies/clinical trials
  - Immunogenicity as a marker of safety
  - Other (provide explanation)
- 

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
  - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
  - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
  - Dose-response study or clinical trial performed for effectiveness
  - Nonclinical study, not safety-related (specify)
- 
- Other
- 

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

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**PMR/PMC Development Coordinator:**

*This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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(signature line for BLAs)

## PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for *each* PMR/PMC in the Action Package.

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NDA/BLA # 203100  
Product Name: Stribild (fixed-dose combination tablet of elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate) 150/150/200/300 mg

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PMR/PMC Description: **1919-2:** Conduct a pediatric pharmacokinetic, safety, and antiviral activity trial of Stribild with activity based on the results of HIV-1 RNA virologic response and safety monitoring over at least 48 weeks of dosing in pediatric subjects from 6 to <12 years of age. Dose selection must be based on pharmacokinetic data for component drugs and must be discussed with FDA prior to initiation of trial. Include in the trial safety monitoring assessment of potential renal toxicity (serial assessments of serum creatinine, serum phosphate, urine glucose, urine protein, calculated creatinine clearance, glomerular filtration rate (GFR) by cystatin C, and calculated fractional excretion of phosphate) and effects on bone (to include serial DEXA assessment).

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PMR/PMC Schedule Milestones:	Final Protocol Submission:	<u>04/2016</u>
	Trial Completion:	<u>09/2018</u>
	Final Report Submission:	<u>12/2018</u>
	Other:	<u>MM/DD/YYYY</u>

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

Adult trials are completed and ready for approval.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

The goal of this trial is to provide PK, safety, and anti-viral activity data in pediatric subjects from 6 to < 12 years of age.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

*If not a PMR, skip to 4.*

– **Which regulation?**

- Accelerated Approval (subpart H/E)  
 Animal Efficacy Rule  
 Pediatric Research Equity Act  
 FDAAA required safety study/clinical trial

– **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?  
 Assess signals of serious risk related to the use of the drug?  
 Identify an unexpected serious risk when available data indicate the potential for a serious risk?

– **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?  
*Do not select the above study/clinical trial type if:* such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?  
*Do not select the above study/clinical trial type if:* the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?  
*Do not select the above study type if:* a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

A nonrandomized, open-label, single-arm, trial of the safety and antiviral activity of the reduced strength STRIBILD in HIV-1 infected, antiretroviral treatment naïve and/or experienced subjects 6 to < 12 years of age

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
  - Pharmacokinetic studies or clinical trials
  - Drug interaction or bioavailability studies or clinical trials
  - Dosing trials
  - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
- 
- Meta-analysis or pooled analysis of previous studies/clinical trials
  - Immunogenicity as a marker of safety
  - Other (provide explanation)
- 

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
  - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
  - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
  - Dose-response study or clinical trial performed for effectiveness
  - Nonclinical study, not safety-related (specify)
- 
- Other
- 

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
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**PMR/PMC Development Coordinator:**

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(signature line for BLAs)

## PMR/PMC Development Template

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NDA/BLA # 203100  
Product Name: Stribild (fixed-dose combination tablet of elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate) 150/150/200/300 mg

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PMR/PMC Description: **1919-3:** Evaluate inhibition by the components of Stribild of the hepatic transporters OATP1B1, OATP1B3, OCT1, and BSEP and evaluate transport of the hepatically eliminated components of Stribild (EVG and COBI) by the hepatic transporters OATP1B1, OATP1B3, and OCT1.

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PMR/PMC Schedule Milestones: Final Protocol Submission: 09/2012  
Study Completion: 11/2012  
Final Report Submission: 12/2012  
Other: \_\_\_\_\_

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

During the clinical review of Stribild, an increase in renal adverse events was noted in the arms receiving both COBI and TDF, compared to the TDF arms without COBI. Evaluation of the hepatic transporters may help elucidate the possible mechanisms for the increased renal adverse events observed when Stribild is administered.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

The nonclinical study should evaluate the drug/drug interaction for all components of Stribild, but COBI and TDF, in particular. The data may help elucidate whether COBI and TDF interact and thereby provide a mechanistic explanation for the increased renal adverse events observed with Stribild.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

*If not a PMR, skip to 4.*

- **Which regulation?**

- Accelerated Approval (subpart H/E)  
 Animal Efficacy Rule  
 Pediatric Research Equity Act  
 FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?  
 Assess signals of serious risk related to the use of the drug?  
 Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?  
*Do not select the above study/clinical trial type if:* such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?  
*Do not select the above study/clinical trial type if:* the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?  
*Do not select the above study type if:* a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

*In vitro* inhibition and transport of the components of Stribild by hepatic transporters.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
  - Pharmacokinetic studies or clinical trials
  - Drug interaction or bioavailability studies or clinical trials
  - Dosing trials
  - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
- 
- Meta-analysis or pooled analysis of previous studies/clinical trials
  - Immunogenicity as a marker of safety
  - Other (provide explanation)
- 

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
  - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
  - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
  - Dose-response study or clinical trial performed for effectiveness
  - Nonclinical study, not safety-related (specify)
- 
- Other
- 

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
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**PMR/PMC Development Coordinator:**

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## PMR/PMC Development Template

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NDA/BLA # 203100  
Product Name: Stribild (fixed-dose combination tablet of elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate) 150/150/200/300 mg

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PMR/PMC Description: **1919-4:** Evaluate inhibition by the components of Stribild of the renal transporters OCT2, MATE1, OAT1, OAT3, MRP2 and MRP4 and evaluate transport of the renally eliminated components of Stribild (FTC and TFV) by the renal transporters OCT2, OAT1, OAT3 and MRP2.

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PMR/PMC Schedule Milestones: Final Protocol Submission: 09/2012  
Study Completion: 11/2012  
Final Report Submission: 12/2012  
Other: \_\_\_\_\_

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

During the clinical review of STRIBILD, an increase in renal adverse events was noted in the arms receiving both COBI and TDF, compared to the TDF arms without COBI. Evaluation of drug effects and drug interactions at the level of renal transporters may help elucidate the possible mechanisms for the increased renal adverse events observed when STRIBILD is administered.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

The nonclinical study should evaluate the drug/drug interaction at the renal level for all components of Stribild, but COBI and TDF, in particular. The data may help elucidate whether COBI+TDF interact and thereby provide a mechanistic explanation for the increased renal adverse events observed with Stribild .

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

*If not a PMR, skip to 4.*

- **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?  
*Do not select the above study/clinical trial type if:* such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?  
*Do not select the above study/clinical trial type if:* the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?  
*Do not select the above study type if:* a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

*In vitro* inhibition and transport of the components of Stribild by renal transporters.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
  - Pharmacokinetic studies or clinical trials
  - Drug interaction or bioavailability studies or clinical trials
  - Dosing trials
  - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
- 
- Meta-analysis or pooled analysis of previous studies/clinical trials
  - Immunogenicity as a marker of safety
  - Other (provide explanation)
- 

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
  - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
  - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
  - Dose-response study or clinical trial performed for effectiveness
  - Nonclinical study, not safety-related (specify)
- 
- Other
- 

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
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**PMR/PMC Development Coordinator:**

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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(signature line for BLAs)

## PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for *each* PMR/PMC in the Action Package.

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NDA/BLA # 203100  
Product Name: Stribild (fixed-dose combination tablet of elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate) 150/150/200/300 mg

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PMR/PMC Description: **1919-5:** Evaluate whether components of Stribild are transported by or inhibit by Pgp and Breast Cancer Resistance Protein (BCRP).

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PMR/PMC Schedule Milestones: Final Protocol Submission: 09/2012  
Study Completion: 11/2012  
Final Report Submission: 12/2012  
Other: \_\_\_\_\_

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

During the clinical review of Stribild, an increase in renal adverse events was noted in the arms receiving both COBI and TDF, compared to the TDF arms without COBI. Evaluation of Pgp and BCRP may help elucidate the possible mechanisms for the increased renal adverse events observed when Stribild is administered.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

The nonclinical study should evaluate the drug/drug interaction for all components of Stribild, but COBI and TDF, in particular. The data may help elucidate whether COBI and TDF interact and thereby provide a mechanistic explanation for the increased renal adverse events observed with Stribild.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

***If not a PMR, skip to 4.***

- **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?  
***Do not select the above study/clinical trial type if:*** such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?  
***Do not select the above study/clinical trial type if:*** the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?  
***Do not select the above study type if:*** a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

<i>In vitro</i> inhibition and transport of the components of Stribild by Pgp and BCRP.
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Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
  - Pharmacokinetic studies or clinical trials
  - Drug interaction or bioavailability studies or clinical trials
  - Dosing trials
  - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
- 
- Meta-analysis or pooled analysis of previous studies/clinical trials
  - Immunogenicity as a marker of safety
  - Other (provide explanation)
- 

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
  - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
  - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
  - Dose-response study or clinical trial performed for effectiveness
  - Nonclinical study, not safety-related (specify)
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- Other
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5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
  - Are the objectives clear from the description of the PMR/PMC?
  - Has the applicant adequately justified the choice of schedule milestone dates?
  - Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?
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**PMR/PMC Development Coordinator:**

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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(signature line for BLAs)

## PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for *each* PMR/PMC in the Action Package.

---

NDA/BLA # 203100  
Product Name: Stribild (fixed-dose combination tablet of elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate) 150/150/200/300 mg

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PMR/PMC Description: **1919-6:** Assess possible cobicistat protease inhibitory activity in vivo by sequencing the protease in virologic failure subjects' isolates from Studies GS-US-236-0102, GS-US-236-0103, GS-US-236-0121, GS-US-236-0123 and GS-US-236-0128.

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PMR/PMC Schedule Milestones:	Final Protocol Submission:	<u>12/2012</u>
	Study Completion:	<u>10/2016</u>
	Final Report Submission:	<u>02/2017</u>
	Other:	_____

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

The sponsor proposes to use cobicistat as a PK enhancer in the absence of an HIV-1 protease inhibitor in treatment-naïve subjects. Since cobicistat is structurally similar to the approved HIV-1 protease inhibitor ritonavir, the question was whether the *in vivo* data support nonclinical studies that cobicistat does not have any antiviral activity. In the sponsor's clinical trials, a disproportionate number of amino acid substitutions in protease developed on-treatment in the small number of virologic failures from the Stribild arm compared to the Atripla arm. The sponsor needs long term follow-up of these studies to better address the question of cobicistat's protease activity.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

*If not a PMR, skip to 4.*

- **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?  
*Do not select the above study/clinical trial type if:* such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?  
*Do not select the above study/clinical trial type if:* the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?  
*Do not select the above study type if:* a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Assess possible cobicistat protease inhibitory activity in vivo by sequencing the protease in virologic failure subjects' isolates from ongoing Studies GS-US-236-0102, GS-US-236-0103, GS-US-236-0121, GS-US-236-0123 and GS-US-236-0128.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials
- Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

Long-term data on resistance needed from clinical trials used to support approval

- Meta-analysis or pooled analysis of previous studies/clinical trials
- Immunogenicity as a marker of safety
- Other (provide explanation)  
Pooled analysis of long-term data on protease resistance development from multiple clinical trials needed

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
- Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
- Dose-response study or clinical trial performed for effectiveness
- Nonclinical study, not safety-related (specify)

Other

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

**PMR/PMC Development Coordinator:**

*This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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(signature line for BLAs)

## PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for each PMR/PMC in the Action Package.

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NDA/BLA # 203100  
Product Name: Stribild (fixed-dose combination tablet of elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate) 150/150/200/300 mg

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PMR/PMC Description: **1919-7:** Perform a clinical trial to better characterize the incidence of and risk factors for renal adverse events in women. Provide adequate renal monitoring in the proposed trial to assess renal safety employing a renal monitoring algorithm similar to that used in GS-US-236-0102 and GS-US-236-0103. The algorithm will include an assessment of serum creatinine, creatinine clearance by Cockcroft-Gault, glomerular filtration rate (GFR) by cystatin C, serum phosphate, renal phosphate threshold (TmP/GFR), urine protein and urine glucose. The trial will enroll approximately 500 women, in order to assess the relative incidence of and risk factors for renal adverse events in women as compared to men enrolled in other Stribild clinical trials.

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PMR/PMC Schedule Milestones:	Final Protocol Submission:	10/2012
	Trial Completion:	07/2016
	Final Report Submission:	11/2016
	Other:	_____

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

A renal safety signal (proximal tubulopathy) was noted in < 1% of study participants in the Phase 3 trials of Stribild (GS-US-236-0102 and GS-US-236-0103).

However, the Phase 3 trials in support of Stribild enrolled only 10% women, thus making the assessment of renal safety in this population unreliable. Moreover, it is possible, based on the totality of the data submitted in support of NDA 203-100 (including summary data from clinical trials not yet fully reviewed), that the renal toxicity (including proximal tubulopathy) may be more prevalent in women. Proximal tubulopathy was observed in 7/918 males (0.8%) and in 2/127 females (1.6%).

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

The goal of this trial is to better characterize the incidence of and risk factors for renal toxicity in women. As noted in our response to Question #1 above, it is possible, based on our review of the totality of the data submitted in support of NDA 203-100 (including summary data from clinical trials not yet fully reviewed), that the renal toxicity (including proximal tubulopathy) may be more prevalent in women.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

*If not a PMR, skip to 4.*

– **Which regulation?**

- Accelerated Approval (subpart H/E)  
 Animal Efficacy Rule  
 Pediatric Research Equity Act  
 FDAAA required safety study/clinical trial

– **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?  
 Assess signals of serious risk related to the use of the drug?  
 Identify an unexpected serious risk when available data indicate the potential for a serious risk?

– **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?  
*Do not select the above study/clinical trial type if:* such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?  
*Do not select the above study/clinical trial type if:* the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?  
*Do not select the above study type if:* a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

A Phase 3b randomized, double-blind trial to evaluate the safety and efficacy of Stribild versus Truvada plus atazanavir boosted with ritonavir in HIV-1 infected treatment naïve women.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
  - Pharmacokinetic studies or clinical trials
  - Drug interaction or bioavailability studies or clinical trials
  - Dosing trials
  - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
- 
- Meta-analysis or pooled analysis of previous studies/clinical trials
  - Immunogenicity as a marker of safety
  - Other (provide explanation)
- 

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
  - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
  - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
  - Dose-response study or clinical trial performed for effectiveness
  - Nonclinical study, not safety-related (specify)
- 
- Other
- 

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

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**PMR/PMC Development Coordinator:**

*This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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## PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for *each* PMR/PMC in the Action Package.

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NDA/BLA # 203100  
Product Name: Stribild (fixed-dose combination tablet of elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate) 150/150/200/300 mg

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PMR/PMC Description: **1919-8:** Conduct a pharmacokinetic (PK) sub-trial of the renal safety trial in women to evaluate the potential for a drug-drug interaction between Stribild and commonly used oral contraceptives. Intensive pharmacokinetic data on each oral contraceptive, when given alone and when co-administered with Stribild, should be collected in an adequate number of subjects.

Note: A renal safety trial in women will be requested as a separate PMR.

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PMR/PMC Schedule Milestones:	Final Protocol Submission:	<u>10/2012</u>
	Trial Completion:	<u>07/2016</u>
	Final Report Submission:	<u>11/2016</u>
	Other:	_____

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

Oral contraceptives are a convenient option for contraception and widely used in the HIV-infected population. The results from a drug-drug interaction trial of Stribild and Ortho Tricyclen Lo showed a significant increase in the exposure of the progestational component. Due to the safety concerns associated with increase in exposure of the progestational component, drug-drug interaction information of Stribild with other commonly used oral contraceptives will provide information on the safe and effective use of the combination.

Although the results of the trial will affect a sub-population of HIV infected patients who may concomitantly take Stribild and oral contraceptives (other than Ortho Tricyclen Lo), the results will NOT impact the safe and effective use of the combination in patients who are not concomitantly taking Stribild and oral contraceptives.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

The review issue is that drug-drug interaction information between Stribild and some of the commonly used oral contraceptives is not available.

The results of the drug-drug interaction trial of Stribild and Ortho Tricyclen Lo showed a significant increase in the systemic exposure of the progestational component (norgestimate). The effect of increase in the progestational component is not fully known and can include increased risk of insulin resistance, dyslipidemia, acne, and venous thrombosis.

The results from an in vivo drug-drug interaction trial between Stribild and other commonly used oral contraceptives will provide quantitative drug-drug interaction information for the safe and effective use of the “Stribild-oral contraceptive” combination in HIV infected patients.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

*If not a PMR, skip to 4.*

- **Which regulation?**

- Accelerated Approval (subpart H/E)  
 Animal Efficacy Rule  
 Pediatric Research Equity Act  
 FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?  
 Assess signals of serious risk related to the use of the drug?  
 Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?  
*Do not select the above study/clinical trial type if:* such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?  
*Do not select the above study/clinical trial type if:* the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?  
*Do not select the above study type if:* a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

The in vivo drug-drug interaction trial will be conducted in HIV-1 infected women and will evaluate changes in the systemic exposure of the progestational and estrogen component, when STRIBILD is co-administered with commonly used oral contraceptives.

Required

- Observational pharmacoepidemiologic study  
 Registry studies  
 Primary safety study or clinical trial  
 Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety  
 Thorough Q-T clinical trial  
 Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)  
 Pharmacokinetic studies or clinical trials  
 Drug interaction or bioavailability studies or clinical trials  
 Dosing trials  
 Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

- 
- Meta-analysis or pooled analysis of previous studies/clinical trials  
 Immunogenicity as a marker of safety  
 Other (provide explanation)
- 

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)  
 Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)  
 Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E  
 Dose-response study or clinical trial performed for effectiveness  
 Nonclinical study, not safety-related (specify)

- 
- Other
- 

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?  
 Are the objectives clear from the description of the PMR/PMC?  
 Has the applicant adequately justified the choice of schedule milestone dates?  
 Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

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**PMR/PMC Development Coordinator:**

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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(signature line for BLAs)

## PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for *each* PMR/PMC in the Action Package.

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NDA/BLA # 203100  
Product Name: Stribild (fixed-dose combination tablet of elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate) 150/150/200/300 mg

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PMR/PMC Description: **1919-9:** A clinical trial to evaluate the drug-drug interaction between Stribild and telaprevir

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PMR/PMC Schedule Milestones:	Final Protocol Submission:	11/2012
	Trial Completion:	09/2013
	Final Report Submission:	10/2013
	Other:	_____

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

There is a theoretical concern regarding increase in the systemic exposure of telaprevir, a substrate of CYP3A enzymes, when co-administered with Stribild, an inhibitor of CYP3A enzymes. In addition, telaprevir is an inhibitor of CYP3A enzymes, therefore, telaprevir can increase in the systemic exposure of elvitegravir and cobicistat, components of Stribild.

Drug-drug interaction information is available for the concomitant use of Stribild with commonly used non-HIV drugs. The results of the drug-drug interaction trial of Stribild and telaprevir will provide information regarding the safe and effective use of the combination.

Although the results of the trial will affect a sub-population of HIV infected patients who may concomitantly take Stribild and telaprevir, the results will NOT impact the safe and effective use of Stribild in patients who are not concomitantly taking Stribild and telaprevir.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

The review issue is that drug-drug interaction information between Stribild and direct acting anti HCV drugs (for example telaprevir) is not available.

The risk associated with concomitant administration of Stribild and telaprevir is that telaprevir exposures can be higher than the telaprevir exposures for which a safety profile is established. Further, when Stribild is co-administered with telaprevir, elvitegravir and cobicistat exposures can be higher than the elvitegravir and cobicistat exposures for which a safety profile is established.

The results from an in vivo drug-drug interaction trial between Stribild and telaprevir will provide quantitative drug-drug interaction information for the safe and effective use of the combination in patients who are co-infected with HIV and Hepatitis C (HCV).

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

*If not a PMR, skip to 4.*

- **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?  
*Do not select the above study/clinical trial type if:* such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?  
*Do not select the above study/clinical trial type if:* the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?  
*Do not select the above study type if:* a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

The in vivo drug-drug interaction trial will be conducted in healthy volunteers and will evaluate changes in the systemic exposure of telaprevir and components of STRIBILD, when telaprevir is co-administered with STRIBILD.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
  - Pharmacokinetic studies or clinical trials
  - Drug interaction or bioavailability studies or clinical trials
  - Dosing trials
  - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
- 
- Meta-analysis or pooled analysis of previous studies/clinical trials
  - Immunogenicity as a marker of safety
  - Other (provide explanation)
- 

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
  - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
  - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
  - Dose-response study or clinical trial performed for effectiveness
  - Nonclinical study, not safety-related (specify)
- 
- Other
- 

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

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**PMR/PMC Development Coordinator:**

*This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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(signature line for BLAs)

## PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for *each* PMR/PMC in the Action Package.

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NDA/BLA # 203100  
Product Name: Stribild (fixed-dose combination tablet of elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate) 150/150/200/300 mg

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PMR/PMC Description: **1919-10:** A clinical trial to evaluate the drug-drug interaction between Stribild and buprenorphine/naloxone

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PMR/PMC Schedule Milestones: Final Protocol Submission: 01/2011  
Trial Completion: 09/2012  
Final Report Submission: 01/2013  
Other: \_\_\_\_\_

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

There is a theoretical concern regarding increase in the systemic exposure of buprenorphine, a substrate of CYP3A enzymes, when co-administered with STRIBILD, an inhibitor of CYP3A enzymes.

Drug-drug interaction information is available for the concomitant use of STRIBILD with commonly used non-HIV drugs. The results of the drug-drug interaction trial of STRIBILD and buprenorphine/naloxone will provide information regarding the safe and effective use of the combination.

Although the results of the trial will affect a sub-population of HIV infected patients who may concomitantly take Stribild and buprenorphine/naloxone, the results will NOT impact the safe and effective use Stribild in patients who are not concomitantly taking STRIBILD and buprenorphine/naloxone.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

The review issue is that drug-drug interaction information between Stribild and buprenorphine/naloxone is not available.

The risk associated with concomitant administration of Stribild and buprenorphine/naloxone is that buprenorphine exposures can be higher than the buprenorphine exposures for which a safety profile is established.

The results from an in vivo drug-drug interaction trial between Stribild and buprenorphine/naloxone will provide quantitative drug-drug interaction information for the safe and effective use of the combination.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

*If not a PMR, skip to 4.*

- **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?  
*Do not select the above study/clinical trial type if:* such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?  
*Do not select the above study/clinical trial type if:* the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?  
*Do not select the above study type if:* a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

The in vivo drug-drug interaction trial will be conducted in healthy volunteers and will evaluate changes in the systemic exposure of buprenorphine, when buprenorphine/naloxone is co-administered with Stribild.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
  - Pharmacokinetic studies or clinical trials
  - Drug interaction or bioavailability studies or clinical trials
  - Dosing trials
  - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
- 
- Meta-analysis or pooled analysis of previous studies/clinical trials
  - Immunogenicity as a marker of safety
  - Other (provide explanation)
- 

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
  - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
  - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
  - Dose-response study or clinical trial performed for effectiveness
  - Nonclinical study, not safety-related (specify)
- 
- Other
- 

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

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**PMR/PMC Development Coordinator:**

*This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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## PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for *each* PMR/PMC in the Action Package.

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NDA/BLA # 203100  
Product Name: Stribild (fixed-dose combination tablet of elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate) 150/150/200/300 mg

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PMR/PMC Description: **1919-11:** A clinical trial to evaluate the drug-drug interaction between Stribild and methadone

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PMR/PMC Schedule Milestones: Final Protocol Submission: 01/2011  
Trial Completion: 09/2012  
Final Report Submission: 01/2013  
Other: \_\_\_\_\_

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

There is a theoretical concern regarding increase in the systemic exposure of methadone, a substrate of CYP3A enzymes, when co-administered with Stribild, an inhibitor of CYP3A enzymes.

Drug-drug interaction information is available for the concomitant use of Stribild with commonly used non-HIV drugs. The results of the drug-drug interaction trial of Stribild and methadone will provide information regarding the safe and effective use of the combination.

Although the results of the trial will affect a sub-population of HIV infected patients who may concomitantly take Stribild and methadone, the results will NOT impact the safe and effective use of Stribild in patients who are not concomitantly taking Stribild and methadone.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

The review issue is that drug-drug interaction information between Stribild and methadone is not available.

The risk associated with concomitant administration of Stribild and methadone is that methadone exposures can be higher than the methadone exposures for which a safety profile is established.

The results from an in vivo drug-drug interaction trial between Stribild and methadone will provide quantitative drug-drug interaction information for the safe and effective use of the combination.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

*If not a PMR, skip to 4.*

- **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?  
*Do not select the above study/clinical trial type if:* such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?  
*Do not select the above study/clinical trial type if:* the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?  
*Do not select the above study type if:* a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

The in vivo drug-drug interaction trial will be conducted in healthy volunteers and will evaluate changes in the systemic exposure of methadone, when methadone is co-administered with STRIBILD.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
  - Pharmacokinetic studies or clinical trials
  - Drug interaction or bioavailability studies or clinical trials
  - Dosing trials
  - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
- 
- Meta-analysis or pooled analysis of previous studies/clinical trials
  - Immunogenicity as a marker of safety
  - Other (provide explanation)
- 

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
  - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
  - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
  - Dose-response study or clinical trial performed for effectiveness
  - Nonclinical study, not safety-related (specify)
- 
- Other
- 

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

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**PMR/PMC Development Coordinator:**

*This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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/s/  
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STACEY MIN  
08/24/2012

LINDA L LEWIS  
08/24/2012

**FOOD AND DRUG ADMINISTRATION  
Center for Drug Evaluation and Research  
Office of Prescription Drug Promotion  
Division of Professional Drug Promotion  
Division of Consumer Drug Promotion**

**\*\*\*Pre-decisional Agency Information\*\*\***

**Memorandum**

**Date:** August 3, 2012

**To:** Stacey Min, Regulatory Project Manager  
Division of Antiviral Products (DAVP)

**From:** Jessica Fox, PharmD, Regulatory Review Officer  
Division of Professional Drug Promotion (DPDP)

Kemi Asante, PharmD, Regulatory Review Officer  
Division of Consumer Drug Promotion (DCDP)

**Subject:** NDA 203100  
Stribild (elvitegravir/cobicistat/emtricitabine/tenofovir  
disoproxil fumarate) Tablets, for oral use

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As requested in DAVP's consult dated November 4, 2011, DPDP and DCDP have reviewed the Stribild prescribing information (PI), patient package insert (PPI), and carton and container labeling.

DPDP and DCDP's comments are provided directly below in the proposed substantially complete versions of the PI and PPI sent via email by DAVP on July 20, 2012.

DPDP reviewed the carton and container labeling submitted on July 26, 2012, and available at [\\CDSESUB5\EVSPROD\NDA203100\203100.enx](#), and has no comments at this time.

Thank you for your consult. If you have any questions on the PI or carton and container labeling, please contact Jessica Fox at 6-5329 or at [Jessica.Fox@fda.hhs.gov](mailto:Jessica.Fox@fda.hhs.gov). If you have any questions on the PPI, please contact Kemi Asante at 6-7425 or at [Kemi.Asante@fda.hhs.gov](mailto:Kemi.Asante@fda.hhs.gov).

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/s/

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JESSICA M FOX  
08/03/2012

**Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Medical Policy Initiatives  
Division of Medical Policy Programs**

**PATIENT LABELING REVIEW**

Date: August 2, 2012

To: Debra Birnkrant, MD  
Director  
**Division of Antiviral Products (DAVP)**

Through: LaShawn Griffiths, MSHS-PH, BSN, RN  
Associate Director for Patient Labeling  
**Division of Medical Policy Programs (DMPP)**  
  
Barbara Fuller, RN, MSN, CWOCN  
Team Leader, Patient Labeling  
**Division of Medical Policy Programs (DMPP)**

From: Sharon R. Mills, BSN, RN, CCRP  
Senior Patient Labeling Reviewer  
**Division of Medical Policy Programs (DMPP)**

Subject: DMPP Review of Patient Labeling: Patient Package Insert  
(PPI)

Drug Name (established name): STRIBILD (elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate)

Dosage Form and Route: Tablets, for oral use

Application Type/Number: NDA 203-100

Applicant: Gilead Sciences, Inc.

## 1 INTRODUCTION

On October 27, 2011, Gilead Sciences, Inc. submitted for the Agency's review an Original New Drug Application for STRIBILD (elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate) Tablets for the proposed indication as a complete regimen for the treatment of HIV-1 infection in adults who are antiretroviral treatment-naïve. On November 8, 2011, the Division of Antiviral Products (DAVP) requested that the Division of Medical Policy Programs (DMPP) review the Applicant's proposed Patient Package Insert (PPI).

This review is written in response to a request by DAVP for DMPP to review the Applicant's proposed Patient Package Insert (PPI) for STRIBILD (elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate) Tablets.

## 2 MATERIAL REVIEWED

- Draft STRIBILD (elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate) Tablets Patient Package Insert (PPI) received on July 13, 2012.
- Draft STRIBILD (elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate) Tablets Prescribing Information (PI) received on October 27, 2011, revised by the Review Division throughout the review cycle, and received by DMPP on July 20, 2012.
- Approved EMTRIVA (emtricitabine) capsules and oral solution labeling dated July 23, 2012
- Approved TRUVADA (emtricitabine and tenofovir disoproxil fumarate) Tablets, labeling dated July 16, 2012
- Approved VIREAD (tenofovir disoproxil fumarate) tablets and oral powder labeling dated January 18, 2012.

## 3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6<sup>th</sup> to 8<sup>th</sup> grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8<sup>th</sup> grade reading level. In our review of the PPI the target reading level is at or below an 8<sup>th</sup> grade level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We have reformatted the PPI document using the Verdana font, size 11.

In our review of the PPI we have:

- simplified wording and clarified concepts where possible

- ensured that the PPI is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the PPI is consistent with the approved comparator labeling where applicable.

#### **4 CONCLUSIONS**

The PPI is acceptable with our recommended changes.

#### **5 RECOMMENDATIONS**

- Please send these comments to the Applicant and copy DMPP on the correspondence.
- Our review of the PPI is appended to this memorandum. Consult DMPP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI.

Please let us know if you have any questions.

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/s/  
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SHARON R MILLS  
08/02/2012

BARBARA A FULLER  
08/02/2012

LASHAWN M GRIFFITHS  
08/02/2012

**MEMORANDUM**

**DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH**

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**CLINICAL INSPECTION SUMMARY**

DATE: July 17, 2012

TO: Stacey Min, Pharm.D., Regulatory Health Project Manager  
Adam Sherwat, M.D., Medical Officer  
Division of Antiviral Products

FROM: Antoine El-Hage, Ph.D.  
Good Clinical Practice Assessment Branch  
Division of Good Clinical Practice Compliance  
Office of Scientific Investigations

THROUGH: Susan Leibenhaut, M.D.  
Acting Team Leader  
Good Clinical Practice Assessment Branch  
Division of Good Clinical Practice Compliance  
Office of Scientific Investigations

THROUGH: Susan D. Thompson, M.D.  
Acting Branch Chief  
Good Clinical Practice Assessment Branch  
Division of Good Clinical Practice Compliance  
Office of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: 203-100/0

APPLICANT: Gilead Sciences, Inc.

DRUG: Stribild (elvitegravir/cobicistat/emtricitabine/tenofovir diphosphate fumarate/GS9350)

NME: No

THERAPEUTIC CLASSIFICATION: Standard Review  
INDICATION: Treatment of HIV-1 infected naïve patients  
CONSULTATION REQUEST DATE: December 1, 2011  
DIVISION ACTION GOAL DATE: August 27, 2012  
PDUFA DATE: August 27, 2012

## **I. BACKGROUND:**

Gilead Sciences, Inc. submitted this application for the use of four drugs (one tablet) in the treatment of HIV-1 infected naïve adults. Two clinical trials were submitted in support of the application: Study GS-US-236-0102 and Study GS-US-236-0103.

### **Investigational Drug**

GS-9350 is a new chemical entity that is a structural analogue of ritonavir (RTV) and has been shown to be a mechanism-based inhibitor that irreversibly inhibits CYP3A enzymes with greater specificity than RTV. GS-9350 is being developed as a pharmacoenhancer (booster) to increase the systemic levels of coadministered agents metabolized by CYP3A enzymes, specifically elvitegravir (EVG), and it could be an alternative to ritonavir in combination with EVG and /or with HIV protease inhibitors. Phase 2 trials demonstrated that the combination of a fixed dose of EVG/FTC/TDF/GS-9350 resulted in a sustained virologic response (SVR); i.e., a substantial decrease in the presence of HIV RNA and an increase in CD4 counts. The applicant has coformulated GS-9350 with EVG and the standard-of-care non-nucleoside reverse transcriptase inhibitor (NRTI) backbone emtricitabine/tenofovir disoproxil fumarate (FTC/TDF) into a fixed-dose tablet.

### **Protocol GS-US-236-0102**

The objective of this study was to evaluate the efficacy of a regimen containing elvitegravir/emtricitabine/tenofovir disoproxil fumarate/GS-9350 versus efavirine/emtricitabine/tenofovir disoproxil fumarate in HIV-1 infected, antiretroviral treatment-naïve adult subjects as determined by the proportion of subjects achieving and maintaining confirmed HIV-1 <50 copies/mL through week 48. The secondary objective of this study was to evaluate the efficacy, safety, and tolerability of two treatment regimens through 96 weeks of treatment.

This protocol was a randomized, double-blind, multicenter, active-controlled study to evaluate the safety and efficacy of a regimen containing an FDC tablet of EVG/FTC/TDF/GS9350 versus ATR in HIV-1 infected, antiretroviral and treatment-naïve adults. Subjects were randomized in a 1:1 ratio to one of the following two treatment arms:

Treatment Arm 1: Fixed -dose combination tablet of EVG/FTC/TDF/GS-9350 QD= Placebo to match the fixed dose combination tablet of Efavirenz/Emtricitabine/Tenofovir DF (ATR, (Atripla) given once daily at bedtime/QHS) (n=350).

Treatment Arm 2: Atripla QHS+Placebo to match the fixed-dose combination tablet or EVG/FTC/TDF/GS-9350 QD (350).

Randomization was stratified by HIV-1 RNA level (<100,000 copies/mL or >100,000 copies/mL) at screening. Qualifying subjects were adult males or females who were treatment naïve with HIV-RNA levels > 5,000 copies/mL at screening. Screening genotype was required to have shown sensitivity to FTC, TDF, and EFV. Female subjects had to use adequate birth control.

The primary efficacy endpoint was the proportion of subjects achieving and maintaining confirmed HIV-1 RNA < 50 copies/mL through week 48. The secondary efficacy endpoint was the proportion of subjects achieving and maintaining confirmed HIV-1 RNA <50 copies/mL through week 96 and a change from baseline in CD4 cell count at week 48 and 96.

### **Protocol GS-US-236-0103**

The objective of this study was to evaluate the efficacy of a regimen containing elvitegravir/emtricitabine/tenofovir disproxil fumarate/GS-9350 versus ritonavir-boosted atazanavir plus/emtricitabine/tenofovir disproxil fumarate in HIV-1 infected, antiretroviral treatment-naïve adult subjects as determined by the proportion of subjects achieving and maintaining confirmed HIV-1 <50 copies/mL through week 48. The secondary objective of this study was to evaluate the efficacy, safety, and tolerability of two treatment regimens through 96 weeks of treatment.

This protocol was a randomized, double-blind, multicenter, active-controlled study to evaluate the safety and efficacy of a regimen containing an FDC tablet of EVG/FTC/TDF/GS9350 versus ATR/ritonavir (ATR/r) plus FTC/TDF in HIV-1 infected, antiretroviral and treatment-naïve adults. Subjects were randomized in a 1:1 ratio to one of the following two treatment arms:

Treatment Arm 1: Fixed -dose combination tablet of EVG/FTC/TDF/GS-9350 + Placebo to match ATR/r plus FTC/TDFQD (n=350).

Treatment Arm 2: ATV/r +FTC/TDF+ Placebo to match the fixed-dose combination tablet of EVG/FTC/TDF/GS-9350 QD (350).

Randomization was stratified by HIV-1 RNA level (<100,000 copies/mL or >100,000 copies/mL) at screening. Qualifying subjects were adult males or females who were treatment naïve with HIV-RNA levels > 5,000 copies/mL at screening. Screening genotype was required to have shown sensitivity to FTC, TDF and EFV. Female subjects were on adequate birth control.

The primary efficacy endpoint was the proportion of subjects achieving and maintaining confirmed HIV-1 RNA < 50copies/mL through week 48. The secondary efficacy endpoint was the proportion of subjects achieving and maintaining confirmed HIV-1 RNA <50 copies/mL through week 96 and a change from baseline in CD4 cell count at week 48 and 96.

The review division requested inspection of four clinical investigators for two pivotal protocols (two sites enrolling in Study GS-US-236-0102, and two sites enrolling in Study GS-US-236-0103) because data from the two protocols are considered essential to the approval process. These sites were targeted for inspection due to: 1) enrollment of a relatively large number of subjects, high treatment response rates (Schneider in Study 0102, Crofoot in Studies 0102 and 0103, and Dejesus in Study 0103), and 2) the need to determine if sites conducted the trial ethically and were in compliance with GCP and local regulations.

**II. RESULTS (by protocol/site):**

<b>Name of CI, site # and location</b>	<b>Protocol and # of subjects</b>	<b>Inspection Dates</b>	<b>Final Classification</b>
Stefan Schneider, M.D. Site# 0663 Living Hope Clinical Foundation 1043 Elm Ave, Suite #30 Long Beach, CA 90813	GS-US236-0102/ 9 subjects	January 21 to 26, 2012	VAI
Gordon Crofoot, Jr. M.D. Site# 2475 3701 Kirby Drive, Suite #1230 Houston, TX 77098	GS-US 236-0102 / 15 subjects  GS-US 236-0103/ 13 subjects	January 17 to 20, 2012	NAI
Edwin DeJesus, M.D. Site# 0698 Orlando Immunology Center 1701 N. Mills Ave Orlando, FL 32803	GS-US-236-0103 19 subjects	February 21 to March 2, 2012	NAI
Anthony Mills, M.D. Site #2798 9201 Sunset Blvd., Suite #812 Los Angeles, CA 90069	GS –US-236-0102 22 subjects	January 9 to 19, 2012	NAI

Key to Classifications

NAI = No deviations

VAI = Deviation(s) from regulations

OAI = Significant deviations for regulations. Data unreliable.

Pending = Preliminary classification based on e-mail communication from the field; EIR has not been received from the field and complete review of EIR is pending.

Protocol Studies GS-US-236-0102

1. **Stefan Schneider, M.D.**  
**Long Beach, CA 90813**

**a. What Was Inspected:** This inspection was performed as a data audit for NDA 203100. At this site, a total of 12 subjects were screened, and two subjects were reported as screen failures. Nine subjects were randomized, five subjects were terminated early (four due to low GFR and one due to moving out of state and enrolling at another study center). Five subjects are currently on the study. Informed Consent Documents for all subject records were reviewed, and it was verified that subjects signed informed consent prior to enrollment.

A review of the medical records/source documents was conducted. The medical records for 12 subjects were reviewed in detail, including drug accountability records, vital signs, laboratory test results, IRB records, and use of concomitant medications. Source

documents were compared to case report forms and to data listings, to include primary efficacy endpoints and adverse events.

**b. General observations/commentary:** At the conclusion of the inspection, a Form FDA 483 was issued to Dr. Schneider. Our investigation found a protocol violation and failure to report the protocol deviation to the IRB in a timely manner.

**Protocol Violations:**

Review of source documents revealed that the clinical investigator did not adhere to the protocol/investigational plan. One subject met protocol defined inclusion/exclusion criteria, but was continued in the study when a GFR was obtained which required repeating the exclusionary laboratory results or notifying the Medical Monitor. Specifically, Subject 6049 had an estimated glomerular filtration rate (eGFR) of 47 and 46 mL/min at week 2 and week 4 (May 6, 2010 and May 19, 2010), respectively. According to the protocol all “subjects with estimated GFR < 50mL/min must have serum creatinine and subject weight measured again within 3 calendar days of receipt of results. If a subject has confirmed estimated GFR < 50 mL/min, the Medical Monitor should be notified and investigational medicinal product discontinued.” The subject was continued on treatment contrary to the protocol withdrawal criteria. In addition, there was no documentation in the source records demonstrating the subject’s GFR was recalculated during the timeframe specified in the protocol, although the necessary values were recorded (body weight and serum creatinine).

The clinical investigator stated that upon discovery of this oversight he discontinued the subject from the study medication on June 25, 2010.

**Failure to Notify the IRB of Protocol Violations:**

Review of source documents revealed the clinical investigator did not notify the IRB of the protocol violation noted above in a timely manner. Subject 6049 was continued in the study despite the fact that the estimated GFR was low enough to require repeating, notification of the Medical Monitor, and withdrawal from the study. This protocol deviation was not reported to the IRB in a timely manner. According to the protocol Section 6.11, “the clinical investigator must promptly notify the IRB in writing of any protocol deviations....” This notification to the IRB must occur promptly and no later than two weeks from the time of identification of the protocol deviation. The subject was randomized on April 21, 2010, with a GFR in the protocol required level (71 mL/min). However, on May 6, 2010 the estimated GFR was 47mL/min and on May 19, 2010 the estimated GFR was 46 mL/min (Weeks 2 and 4). The IRB was not notified of this protocol violation until December 21, 2011.

The clinical investigator acknowledged the inspectional findings in a written response dated February 13, 2011, in which he promised to implement corrective actions to ensure that the deviations from the investigational plan are properly corrected and reported in a timely manner in the future.

**c. Assessment of Data Integrity:** Although regulatory violations were noted, the findings are not likely to critically impact primary efficacy and safety analyses as they are isolated in nature. OSI does not consider the effect on overall data integrity to be significant. In general, the records reviewed were found to be verifiable with the exceptions as noted above. There were no known limitations to this inspection. The data generated from Dr. Schneider’s site are considered reliable and appear acceptable in support of the application.

Protocol Studies GS-US-236-0102 and 0103

**2. Gordon E. Crofoot, M.D.**  
**Houston, TX 77098**

**a. What Was Inspected:** At this site, for study protocol GS-US-236-0102, a total of 18 subjects were screened, and 3 subjects were reported as screen failures. Fifteen (15) subjects were randomized and one subject was terminated early. Review of the Informed Consent Documents, for all subjects reviewed, verified that subjects signed consent forms prior to enrollment.

The medical records/source data for all 14 subjects were reviewed in depth, including drug accountability records, vital signs, laboratory results, IRB records, prior and current medications, and inclusion/exclusion criteria. Source documents were compared to CRFs and data listings for primary efficacy endpoints and adverse events listing. There was no evidence of inaccuracy of data capture. The study is on-going and none of the subjects have reached Week 96 at the close of the inspection.

For study protocol GS-US-236-0103, a total of 17 subjects were screened, and four subjects were reported as screen failures. Thirteen (13) subjects were randomized, and two subjects were terminated early. Eleven subjects remained active on the study.

The medical records/source data reviewed for all 12 subjects’ files were reviewed in depth, including drug accountability records, consent forms, vital signs, laboratory results, IRB records, prior and current medications, and inclusion/exclusion criteria. Source documents were compared to CRFs and data listings for primary efficacy endpoints and adverse events listing. There was no evidence of inaccuracy of data capture. The study is on-going, and none of the subjects have reached Week 96 at the close of the inspection.

**b. General Observations/Commentary:** At the conclusion of the inspection, no Form FDA 483 was issued to Dr. Crofoot. The medical records reviewed were verifiable based on the information available at the site. There were no known limitations to the inspection. There were no deaths and no under-reporting of adverse events.

**c. Assessment of Data Integrity:** The data submitted in support of clinical efficacy and safety at Dr. Crofoot’s site are considered reliable and appear acceptable in support of the pending application.

Protocol Study GS-US-236-0103

**3. Edwin DeJesus, M.D.  
Orlando, FL 32803**

**a. What Was Inspected:** At this site, a total of 28 subjects were screened, seven subjects were reported as screen failures, 21 subjects were randomized into the study, one subject withdrew consent, and 2 subjects were transferred to other study sites. Eighteen (18) subjects completed 48 weeks of treatment and 18 subjects are continuing with the long term phase of the study. Review of the Informed Consent Documents, for all subjects records reviewed, verified that all subjects signed consent forms prior to enrollment.

The medical records/source documents for 18 subjects were reviewed. The medical records were reviewed in depth, including drug accountability records, vital signs, IRB files, laboratory test results, inclusion/exclusion criteria, and use of concomitant medications. Source documents for subjects were compared to case report forms and data listings, to include primary efficacy endpoints and adverse events.

**b. General Observations/Commentary:** At the conclusion of the inspection, no Form FDA 483 was issued to Dr. DeJesus. Our investigation found minor insignificant observations. For example, medication bottle #100975 was dispensed to Subject 7405 in error which was detected before receiving the correct medication bottle. In addition, for three subjects (7026, 7027 and 7090) there was no documentation that the CD4 counts were completed at least 30 days prior to screening. The clinical investigator acknowledged the findings. These findings were insignificant and had no impact on the data generated from this site. The medical records reviewed were found to be in order and the data verifiable.

**c. Assessment of Data Integrity:** Although regulatory violations were noted, the findings are not likely to critically impact primary efficacy and safety analyses; therefore, OSI does not consider the effect on overall data integrity to be significant. In general, the records reviewed were found to be verifiable with the exceptions as noted above. There were no known limitations to this inspection. The data generated from Dr. DeJesus's site are considered reliable and appear acceptable in support of the application.

**4. Anthony Mills, M.D.  
West Hollywood, CA 90069-3709**

**a. What was Inspected:** At this site, a total of 28 subjects were screened, six subjects were reported as screen failures, and 22 subjects were randomized into the study. Two subjects transferred to another site, and 20 subjects are continuing on the study. Review of Informed Consent Documents for all subjects verified that all subjects signed consent forms prior to enrollment.

The medical records/source data for seven subjects were reviewed. The review included drug accountability records, vital signs, laboratory results, diary cards, IRB files, prior and current medications, inclusion/exclusion criteria, and adverse events. No Form FDA 483 was issued. Source documents for the seven subjects were compared to case report forms and to data listings for primary efficacy endpoint and adverse events.

**b. General Observations/Commentary:** At the conclusion of the inspection, no Form FDA 483 was issued to Dr. Mills. The medical records reviewed were found to be in order and the data verifiable. There were no limitations to the inspection. The study appears to have been conducted adequately at this site.

**c. Assessment of Data Integrity:** The data submitted in support of the clinical efficacy and safety at Dr. Mills' site are considered reliable and appear acceptable in support of the application.

### **III. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS**

Four domestic clinical investigator sites were inspected in support of this application. The inspections of Drs. Crofoot, Dejesus and Mills revealed no regulatory violations, and the final classification for these inspections is No Action Indicated (NAI). While regulatory violations were identified during the inspection of Dr. Schneider, the findings are not likely to critically impact primary efficacy and safety analyses; therefore, OSI does not consider the effect on overall data integrity to be significant. The final classification for the inspection of Dr. Schneider is Voluntary Action Indicated (VAI). Overall, the data submitted from these sites are considered acceptable in support of the pending application.

*{See appended electronic signature page}*

Antoine El-Hage, Ph.D.  
Good Clinical Practice Assessment Branch  
Division of Good Clinical Practice Compliance  
Office of Scientific Investigations

CONCURRENCE:

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Susan Leibenhaut, M.D.  
Acting Team Leader  
Good Clinical Practice Assessment Branch  
Division of Good Clinical Practice Compliance  
Office of Scientific Investigations

*{See appended electronic signature page}*

Susan D. Thompson, M.D.  
Acting Branch Chief  
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/s/  
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ANTOINE N EL HAGE  
07/17/2012

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07/17/2012

SUSAN LEIBENHAUT  
07/17/2012



# Memorandum

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH  
DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS

Date: July 9, 2012

From: CDER DCRP QT Interdisciplinary Review Team

Through: Norman Stockbridge, M.D., Ph.D.  
Division Director  
Division of Cardiovascular and Renal Products /CDER

To: Stacy Min, DAP

Subject: QT-IRT Consult to NDA 203100

This memo responds to your consult to us dated May 30, 2012 regarding proposed labeling for the combination product (Elvitegravir/Cobicistat/Emtricitabine/Tenofovir). The QT-IRT received and reviewed the following materials:

- Your consult
- Proposed label
- IRT review for cobicistat (dated 03/01/2010)
- IRT Review for Elvitegravir (dated 05/16/2007)

## QT-IRT Comments for DAVP

Sponsor has proposed the following language in proposed label:

### Effects on Electrocardiogram

The electrocardiographic effects of cobicistat were determined in a study of 40 healthy adult subjects. Cobicistat did not prolong the QTcF interval at exposures 2- and 4-fold above the recommended therapeutic dose. A modest increase in PR interval (+9.6 msec) occurred around  $C_{max}$ , 3 to 5 hours after dosing. This finding was not considered to be clinically significant.

In a thorough QT/QTc study in 126 healthy subjects, elvitegravir at therapeutic or supratherapeutic doses approximately 2 times the recommended therapeutic dose did not affect the QT/QTc interval and did not prolong the PR interval.

TQT studies have been conducted for cobicistat and elvitegravir. Since TQT studies of two of the components in this regimen or the combination regimen itself have not been conducted, QT-IRT recommends the following labeling language. These are suggestions only and we defer the final labeling decision to the review division.

### **Effects on Electrocardiogram**

TQT studies have been conducted for elvitegravir and cobicistat. The effect of the other two components, tenofovir and emtricitabine, or the combination regimen [TRADE NAME] on the QT interval is not known.

The effect of multiple doses of elvitegravir 125 and 250 mg (co-administered with 100 mg ritonavir) on QTc interval was evaluated in a randomized, placebo- and active- controlled (moxifloxacin 400 mg) parallel group thorough QT study in 126 healthy subjects. In a study with demonstrated ability to detect small effects, the upper bound of the one-sided 95% confidence interval for the largest placebo adjusted, baseline-corrected QTc based on Fridericia's correction method (QTcF) was below 10 ms, the threshold for regulatory concern. The dose of 250 mg elvitegravir (with 100 mg ritonavir) is expected to cover the high exposure clinical scenario.

The effect of single dose of cobicistat 250 mg and 400 mg on QTc interval was evaluated in a randomized, placebo- and active- controlled (moxifloxacin 400 mg) four-period crossover thorough QT study in 48 healthy subjects. In a study with demonstrated ability to detect small effects, the upper bound of the one-sided 95% confidence interval for the largest placebo adjusted, baseline-corrected QTc based on individual correction method (QTcI) was below 10 ms, the threshold for regulatory concern. The dose of 400 mg cobicistat is expected to cover the high exposure clinical scenario. Prolongation of the PR interval was noted in subjects receiving cobicistat in the same study. The maximum mean (95% upper confidence bound) difference in PR from placebo after baseline-correction was 9.5 (12.1) ms for 250 mg dose and 20.2 (22.8) for 400-mg dose cobicistat.

### **BACKGROUND**

The proposed dosing regimen is a fixed dose combination of 150-mg elvitegravir, 150-mg cobicistat, 200-mg emtricitabine, and 300-mg tenofovir disoproxil fumarate. This product will be used as a stand alone therapeutic regimen i.e., PK drug-drug interaction potential with other anti-viral drugs is unlikely. The sponsor has conducted TQT study for individual components cobicistat and elvitegravir and both these studies were negative, i.e., no significant effect on QT interval (see below). The effect of tenofovir and emtricitabine on the QT interval is not known. Furthermore, the sponsor has not conducted a TQT study of the combination regimen. The review division is consulting us on the proposed labeling of the combination regimen.

- Cobicistat and Elvitegravir: Cobicistat is a pharmacoenhancer that could be used as an alternative to ritonavir, in combination with elvitegravir and/or with protease inhibitors for the treatment of HIV infection. No significant QT prolongation effect was seen in the TQT study of cobicistat at dose level of 250 and 400 mg. Furthermore, there was a significant negative concentration-QT relationship; i.e., QT interval decreased with

increase in cobicistat concentrations. The suprathapeutic dose of cobicistat in this TQT study covers the worst case exposure scenario expected with 150 mg cobicistat in this combination product.

Elvitegravir: No significant QT prolongation effect was seen in the TQT study of at dose level of 125 (125 mg elvitegravir with 100-mg ritonavir) and 250 mg (250-mg elvitegravir with 100-mg ritonavir). The increase in exposure of elvitegravir with ritonavir is similar to what is expected when elvitegravir is given with cobicistat. The suprathapeutic dose of elvitegravir (with ritonavir) in the TQT study covers the worst case exposure scenario expected with 150 mg elvitegravir in this combination product.

Based on the label, there is no effect of severe renal impairment on PK of elvitegravir and cobicistat. There is no effect of moderate hepatic impairment on PK of cobicistat or elvitegravir. (b) (4)

- Emtricitabine and tenofovir: The QT evaluation has not been conducted for these two components of the combination. The doses used in this fixed dose combination are same as the therapeutic doses in other approved combination products [Complera® (Rilpivirine+Tenofovir 300 mg+Emtricitabine 200 mg), Truvada® (tenofovir 300 mg+emtricitabine 200 mg)].

## Data mining

We conducted an MGPS (Multi-item Gamma Poisson Shrinker) data mining analysis of the AERS database for AE's described under "selection criteria" and related to cardiac arrhythmias with emtricitabine alone or combined with tenofovir and tenofovir single agent.

For tenofovir the EBG (Empirical Bayes Geometric Mean) and EB05 values for AV block, hypokalaemia, long QT syndrome and sudden death were above 2 indicating higher than expected reporting of these events. Higher than expected reporting were also found for emtricitabine (sudden death and ventricular fibrillation) and emtricitabine+tenofovir (sudden death, hypokalaemia and AV block-some of the AV block).

By reviewing cases of sudden death the majority were confounded by concomitant medications that prolong QT (i.e., Kaletra®, opioids) or prolong PR (ritonavir) and co-morbidities (AIDS, diabetes, hypertension, drug dependence, chronic renal disease, and hypokalaemia).

Of note, some AV block reports were in neonates from mothers taking Kaletra (ritonavir+lopinavir) and Truvada (emtricitabine+tenofovir). The 4 reports for Emtricitabine+tenofovir correspond to two cases.

Generic name	PT	Outcome	N	EBGM	EB05	EB95	INTSS	RR	E
Tenofovir	Atrioventricular block complete	Life-threatening	2	5.89	2.01	14.3	0.373	11.6	0.173
Tenofovir	Atrioventricular block complete	Other	7	5.46	2.93	9.50	0.642	7.92	0.884
Tenofovir	Bradycardia foetal	Congenital Anomaly	2	7.13	2.43	17.3	0.466	34.0	0.059
Tenofovir	Hypokalaemia	Died	10	5.82	3.44	9.36	0.493	6.30	1.59
Tenofovir	Hypokalaemia	Disabled	4	5.79	2.58	11.6	0.370	7.14	0.560
Tenofovir	Hypokalaemia	Hospitalized	37	7.98	6.06	10.4	0.869	8.28	4.47
Tenofovir	Hypokalaemia	Life-threatening	7	7.34	3.93	12.8	0.563	8.79	0.796
Tenofovir	Hypokalaemia	Other	40	8.69	6.67	11.2	0.956	9.03	4.43
Tenofovir	Long QT syndrome	Life-threatening	1	10.5	2.70	30.8	0.233	55.9	0.018
Tenofovir	Sudden death	Died	7	5.23	2.80	9.09	0.331	5.39	1.30

Generic name	PT	Outcome	N	EBGM	EB05	EB95	INTSS	RR	E
Emtricitabine	Sudden death	Died	2	7.62	2.60	18.5	0.308	11.2	0.179
Emtricitabine	Ventricular fibrillation	Died	3	7.33	2.93	15.9	0.685	19.8	0.152
Emtricitabine And Tenofovir	Atrioventricular block complete	Congenital Anomaly	4	18.5	7.96	40.3	1.13	121.1	0.033
Emtricitabine And Tenofovir	Hypokalaemia	Hospitalized	20	6.41	4.41	9.07	1.19	7.45	2.68
Emtricitabine And Tenofovir	Hypokalaemia	Life-threatening	6	6.96	3.55	12.6	0.958	14.3	0.420
Emtricitabine And Tenofovir	Sudden death	Died	5	7.90	3.81	14.9	0.451	9.18	0.544

Dimension: 3 Selection Criteria: Generic name(Emtricitabine, Emtricitabine And Rilpivirine And Tenofovir, Emtricitabine And Tenofovir) + PT(, Accelerated idioventricular rhythm, Anomalous atrioventricular excitation, Arrhythmia, Arrhythmia supraventricular, Athletic heart syndrome, Atrial fibrillation, Atrial flutter, Atrioventricular block, Atrioventricular block complete, Atrioventricular block first degree, Atrioventricular block second degree, Atrioventricular conduction time shortened, Atrioventricular dissociation, Atrioventricular extrasystoles, Bifascicular block, Bradycardia, Bradycardia foetal, Bradycardia neonatal, Bundle branch block, Bundle branch block bilateral, Bundle branch block left, Bundle branch block right, Cardiac arrest, Cardiotoxicity, Convulsion, Electrocardiogram PQ interval, Electrocardiogram PQ interval prolonged, Electrocardiogram PR interval, Electrocardiogram PR prolongation, Electrocardiogram PR shortened, Electrocardiogram Q wave abnormal, Electrocardiogram Q waves, Electrocardiogram Q waves normal, Electrocardiogram QRS complex, Electrocardiogram QRS complex prolonged, Electrocardiogram QRS complex shortened, Electrocardiogram QT interval, Electrocardiogram QT interval abnormal, Electrocardiogram QT prolonged, Electrocardiogram QT shortened, Electrocardiogram RR interval prolonged, Electrocardiogram T wave abnormal, Electrocardiogram T wave amplitude decreased, Electrocardiogram T wave amplitude increased, Electrocardiogram T wave biphasic, Electrocardiogram T wave inversion, Electrocardiogram U wave inversion, Electrocardiogram U-wave abnormality, Electrocardiogram U-wave biphasic, Electrocardiogram abnormal, Electrocardiogram ambulatory abnormal, Electrocardiogram repolarisation abnormality, Heart rate, Heart rate abnormal, Heart rate decreased, Heart rate increased, Hypokalaemia, Hypomagnesaemia, Long QT syndrome, Palpitations, Presyncope, Sinus arrhythmia, Sinus bradycardia, Sinus tachycardia, Sudden cardiac death, Sudden death, Syncope, Tachyarrhythmia, Tachycardia, Torsade de pointes, Ventricular arrhythmia, Ventricular asystole, Ventricular extrasystoles, Ventricular fibrillation, Ventricular flutter, Ventricular tachyarrhythmia, Ventricular tachycardia, Wolff-Parkinson-White syndrome) + Outcome Where: EB05 > 2.0

Notes	
ID:	7972
Type:	MGPS
Name:	3D Generic (S), PT and Outcome
Description:	Generic, PT and Outcome; Suspect drugs only; 3D; Minimum count=1; Standard strata (Age, FDA Year, Gender); no PRR or ROR; includes hierarchy information
Project:	CBAERS Standard Runs
Configuration:	CBAERS BestRep (S) (v2)
Configuration description:	CBAERS data; best representative cases; suspect drugs only; with duplicate removal
As of date:	06/21/2012 00:00:00
Item variables:	Generic name, PT, Outcome
Stratification variables:	Standard strata
Event Hierarchy:	MedDRA 15.0
Highest dimension:	3
Minimum count:	1
Calculate PRR:	No
Calculate ROR:	No
Fill in hierarchy values:	Yes
Exclude single itemtypes:	Yes
Fit separate distributions:	Yes
Save intermediate files:	No
Created by:	Empirica Signal Administrator
Created on:	06/28/2012 12:49:59 EDT
User:	Monica Fiszman
Source database:	Source Data: CBAERS data from Extract provided by CBER as of 06/21/2012 00:00:00 loaded on 2012-06-27 16:37:32.0

Thank you for requesting our input into the development of this product under NDA. We welcome more discussion with you now and in the future. Please feel free to contact us via email at [cderderpqt@fda.hhs.gov](mailto:cderderpqt@fda.hhs.gov)

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NITIN MEHROTRA  
07/09/2012

MONICA L FISZMAN  
07/09/2012

NORMAN L STOCKBRIDGE  
07/09/2012

**Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Surveillance and Epidemiology  
Office of Medication Error Prevention and Risk Management**

**Label, Labeling and Packaging Review**

Date: June 28, 2012

Reviewer: Morgan Walker, Pharm.D., M.B.A.  
Division of Medication Error Prevention and Analysis

Acting Team Leader: Jamie Wilkins Parker, Pharm.D.  
Division of Medication Error Prevention and Analysis

Director: Carol Holquist, RPh.  
Division of Medication Error Prevention and Analysis

Drug Name and Strength: Stribild  
(Elvitegravir, Cobicistat, Emtricitabine, and  
Tenofovir Disoproxil Fumarate) Tablets  
150 mg/150 mg/200 mg/300 mg

Application Type/Number: NDA 203100

Applicant: Gilead Sciences, Inc.

OSE RCM #: 2011-4540

\*\*\* This document contains proprietary and confidential information that should not be released to the public.\*\*\*

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## **1 INTRODUCTION**

This review evaluates the proposed container label, carton and insert labeling for Stribild (Elvitegravir, Cobicistat, Emtricitabine, and Tenofovir Disoproxil Fumarate) Tablets, NDA 203100, for areas of vulnerability that could lead to medication errors.

### **1.1 BACKGROUND AND REGULATORY HISTORY**

The proposed proprietary name, Stribild, was submitted on March 29, 2012 and was found acceptable in OSE Review # 2012-758 (NDA 203100), dated June 12, 2012.

### **1.2 PRODUCT INFORMATION**

The following product information is provided in the December 13, 2011 submission.

- Active Ingredient: Elvitegravir/Cobicistat/Emtricitabine/Tenofovir Disoproxil Fumarate
- Indication of Use: Treatment of HIV-1 infection in adults who are antiretroviral treatment-naïve or who have no known substitutions associated with resistance to the individual components of the product
- Route of Administration: Oral
- Dosage Form: Tablets
- Strength: 150 mg/150 mg/200 mg/300 mg
- Dose: One tablet once daily with food
- How Supplied: 30-count bottles
- Storage: Store at 25°C (77°F); excursions permitted 15°C to 30°C (59°F to 86°F) [See USP Controlled Room Temperature].
- Container and Closure Systems: HDPE bottle with child resistant cap

## **2 METHODS AND MATERIALS REVIEWED**

Using the principals of human factors and Failure Mode and Effects Analysis,<sup>1</sup> along with post marketing medication error data, the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the following:

- Container Labels submitted December 13, 2011 (Appendix A)
- Carton Labeling submitted December 13, 2011 (Appendix B)
- Insert Labeling submitted December 13, 2011

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<sup>1</sup> Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

### **3 MEDICATION ERROR RISK ASSESSMENT**

A review of the retail and Gilead Access Program container labels, as well as the carton and insert labeling identified the following discrepancies:

- A. Retail and Gilead Access Program container labels, Gilead Access Program carton labeling, and insert labeling:
  - 1. The name “TRADENAME” which is located in the space where the trade name will placed is in all capital letters. Presenting the trade name in all capital letters decreases readability.
  - 2. The established name is not at least ½ the size of the proprietary name.
  - 3. There is inconsistency with the storage recommendations presented in the insert labeling and the container label and carton labeling. The Gilead Access Program container label and carton labeling present the storage recommendation as “Store below 30°C (86°F)”, however, the retail container label presents the storage recommendation as “Store at 25°C (77°F) (see insert)”.
- B. Retail container labels:
  - The “Keep out of the reach of children” statement is missing.

### **4 CONCLUSIONS**

DMEPA concludes that the proposed container labels and carton labeling can be improved to increase the readability and prominence of important information on the label to mitigate any confusion.

### **5 RECOMMENDATIONS**

Based on this review, DMEPA recommends the following be implemented prior to approval of this NDA:

- A. Retail and Gilead Access Program container labels, and Gilead Access Program carton labeling:
  - 1. Ensure that the trade name is placed in title case instead of all capital letters for improved readability.
  - 2. Ensure the established name is at least ½ the size of the proprietary name, taking into account all pertinent factors including typography, layout, contrast and other printing features as per 21 CFR 201.10(g)(2).
  - 3. Clarify the product storage recommendations, which should be presented consistently on the container labels, carton and insert labeling across the product line, as they currently state “Store below 30°C (86°F)” on the Gilead Access Program container label and carton labeling and “Store at 25°C (77°F) (see insert)” on the retail container label.

B. Retail container labels:

- Place a “Keep out of the reach of children” statement on the side panel of the retail container to be consistent with the Gilead Access Program container label.

If you have further questions or need clarifications, please contact Brantley Dorch, project manager, at 301-796-0150.

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

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MORGAN A WALKER  
06/28/2012

JAMIE C WILKINS PARKER  
06/29/2012

CAROL A HOLQUIST  
06/29/2012

## CDER/DRUP Consultation Response (Tracking No. 314)

<b>Division Consult #</b>	314
<b>To</b>	Stacey Min, RPM Office of Antimicrobial Products Division of Antiviral Products (DAVP)
<b>From</b>	Gerald Willett MD, Medical Officer, Division of Reproductive and Urologic Products (DRUP) through Lisa Soule, MD, Medical Team Leader and Audrey Gassman MD, Acting Deputy Division Director
<b>Name of drug product</b>	elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate (EVG/COBI/FTC/TDF); also called QUAD – NDA 203100
<b>Class of drugs</b>	Combination HIV-1 drug product
<b>Sponsor</b>	Gilead Sciences, Inc. 333 Lakeside Drive Foster City, CA, 94404
<b>Re:</b>	Drug interactions with Oral Contraceptive (OC)
<b>Date of consult request</b>	March 23, 2012
<b>Desired completion date</b>	April 9, 2012

### Background

DAVP is currently reviewing a single tablet regimen for human immunodeficiency virus type 1 (HIV-1) that contains four components, namely:

<b>Quad Components</b>	<b>Notes on component activity and present labeling guidance in regard to oral contraceptives (OCs)</b>
Elvitegravir (EVG) NME	Integrase inhibitor – prevents integration of HIV-1 genetic material into the host-cell genome
Cobicistat (COBI) NME	Inhibits liver enzymes that metabolize elvitegravir thereby obtaining higher concentrations of elvitegravir
Emtricitabine (FTC)	Nucleoside reverse transcriptase inhibitor – inhibits reverse transcriptase, the enzyme that copies HIV RNA into new viral DNA  No OC drug interaction data identified in labels for emtricitabine alone
Tenofovir disoproxil fumarate (TDF)	Nucleotide reverse transcriptase inhibitor – inhibits reverse transcriptase  Label states that there were no changes in C <sub>max</sub> , AUC or C <sub>min</sub> for Ortho Tri-Cyclen (ethinyl estradiol, norgestimate) used with tenofovir alone

The combination product is also referred to as QUAD.

DAVP consulted DRUP in regard to Study GS-US-236-0106, which evaluated the drug-drug interaction of QUAD with a combination oral contraceptive (Ortho Tri-Cyclen Lo) that contains norgestimate (NGM) as the progestin component and ethinyl estradiol (EE) as the estrogenic component.

The Applicant’s findings in Study GS-US-236-0106 were the following:

- Coadministration of QUAD with Ortho Tri-Cyclen Lo (NGM/EE) resulted in the following changes to EE and NGMN\* relative to administration of NGM/EE alone.

Test		Change in EE
AUCtau	area under the plasma/serum/peripheral blood mononuclear cell (PBMC) concentration versus time curve over the dosing interval	Decrease by 25%
Ctau	observed drug concentration at the end of the dosing interval	Decrease by 43%

Test		Change in NGMN*
AUCtau	area under the plasma/serum/PBMC concentration versus time curve over the dosing interval	Increase by 126%
Ctau	observed drug concentration at the end of the dosing interval	Increase by 167%
Cmax	maximum observed plasma/serum/PBMC concentration of drug	Increase by 108%

\* Note: NGMN is norelgestromin, which is the pharmacologically active metabolite of norgestimate

- Comparison of Day 0 to Day 21 changes in pharmacodynamics after administration of NGM/EE + EVG/COBI/FTC/TDF vs. NGM/EE revealed a similar decrease in FSH after both treatments, and a greater reduction in LH after NGM/EE + EVG/COBI/FTC/TDF than after NGM/EE alone. No changes in serum progesterone were observed.



Taking NGM/EE as an oral contraceptive concurrent with EVG/COBI/FTC/TDF treatment is safe and well tolerated.

**Medical Officer’s Comment:**

*The total number of subjects enrolled in this study was 21 and the study duration extended up to 3 menstrual cycles (28 days each). Therefore, it is difficult to make any definitive clinical recommendations regarding contraceptive efficacy and long-term safety (including rare events such as thromboembolic events). In this small study of short duration there were no serious adverse events. Nausea and headache occurred in a small number of subjects.*

**The specific consultation questions and DRUP responses are:**

### **Consultation Questions:**

Question 1. Is the increase in the systemic exposure of NGMN, when Ortho Tri-Cyclen Lo is co-administered with QUAD, clinically relevant?

#### **Consult response:**

**The Division has not detected safety signals that suggest that use of norgestimate-containing combination oral contraceptives (COCs) confers a higher risk than other COCs with respect to the more serious safety issues relevant to COCs, specifically venous thromboembolic events (VTEs). The potential safety impact of increased NGMN concentrations associated with concurrent use of QUAD cannot be determined from the current drug-drug interaction (DDI) study because the study was small and of short duration for a contraceptive product. However, there are no data to suggest that the increased NGMN concentrations observed would have an effect on VTE risk, or that this COC should not be used concomitantly by QUAD users.**

**Increased exposure to the progestin component of the pill relative to the estrogen component could potentially lead to more break-through bleeding (which is more common in progestin-dominant COCs). Labeling should reflect the increased progestin PK findings and that the impact on long-term safety is unknown. A statement could be made in the label that increased progestin concentrations could lead to irregular bleeding and spotting.**

**An adverse effect on efficacy from the increased progestin is unlikely, especially since the progestin component of the pill is considered more important to contraceptive efficacy.** (b) (4)

**The increased progestin exposure along with the evidence of greater LH suppression suggests that the contraceptive efficacy for this product is likely to be unchanged.**

**DRUP recommends** (b) (4)

**the label should describe the PK changes seen when this oral contraceptive is co-administered with QUAD, and leave it to clinicians and patients decide on specific contraceptive options. The labeling should also indicate that DDIs between QUAD and other COCs that contain different progestins have not been evaluated.**

Question 2. If QUAD and Ortho Tri-Cyclen Lo cannot be co-administered, are there other options for oral contraceptive use that may be safer than Ortho Tri-Cyclen Lo?

#### **Consult response:**

**As stated in response to Question 1, DRUP does not anticipate efficacy or major safety issues that would preclude concomitant use of QUAD and Ortho Tri-Cyclen Lo. For prescribers or women who have concerns related to concomitant use of COCs and QUAD, long-acting reversible non-oral contraceptive methods such as**

**intrauterine devices or progestin implants or progestin injections may be worth considering. Use of condoms in addition to another contraceptive method is also an important consideration for HIV-positive women, particularly in those whose partner is HIV-negative.**

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/s/  
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GERALD D WILLETT  
04/11/2012

LISA M SOULE  
04/11/2012

AUDREY L GASSMAN  
04/11/2012

**Clinical Pharmacology**  
**Tracking/Action Sheet for Formal/Informal Consults**

From: Li, Li, Ph.D.

To: DOCUMENT ROOM (LOG-IN and LOG-OUT)  
Please log-in this consult and review action for the  
specified IND/NDA submission

DATE: 03/27/2012

NDA No.: NDA 203100

DATE OF DOCUMENT

03/23/2012

NAME OF DRUG  
Single Tablet Regimen of  
Elvitegravir/Cobicistat/Emtricitabine/Tenofovir  
Disoproxil Fumarate  
(EVG/COBI/FTC/TDF; QUAD)

PRIORITY  
CONSIDERATION

Date of Formal Consult  
from the Division of  
Antiviral Products:

03/23/2012

NAME OF THE SPONSOR: Gilead Sciences, Inc.

**TYPE OF SUBMISSION**

**CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS RELATED ISSUE**

- |  |  |  |
|--|--|--|
| <input type="checkbox"/> PRE-IND                 | <input type="checkbox"/> DISSOLUTION/IN-VITRO RELEASE                                  | <input type="checkbox"/> FINAL PRINTED LABELING                              |
| <input type="checkbox"/> ANIMAL to HUMAN SCALING | <input type="checkbox"/> BIOAVAILABILITY STUDIES                                       | <input type="checkbox"/> LABELING REVISION                                   |
| <input type="checkbox"/> IN-VITRO METABOLISM     | <input type="checkbox"/> IN-VIVO WAIVER REQUEST  | <input type="checkbox"/> CORRESPONDENCE                                      |
| <input type="checkbox"/> PROTOCOL                | <input type="checkbox"/> SUPAC RELATED   | <input type="checkbox"/> DRUG ADVERTISING                                    |
| <input type="checkbox"/> PHASE II PROTOCOL       | <input type="checkbox"/> CMC RELATED   | <input type="checkbox"/> ADVERSE REACTION REPORT                             |
| <input type="checkbox"/> PHASE III PROTOCOL      | <input type="checkbox"/> PROGRESS REPORT   | <input type="checkbox"/> ANNUAL REPORTS                                      |
| <input type="checkbox"/> DOSING REGIMEN CONSULT  | <input type="checkbox"/> SCIENTIFIC INVESTIGATIONS                                     | <input type="checkbox"/> FAX SUBMISSION                                      |
| <input type="checkbox"/> PK/PD- POPPK ISSUES     | <input type="checkbox"/> MEETING PACKAGE (EOP2/Pre-<br>NDA/CMC/Pharmacometrics/Others) | <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW):<br>Consult review |
| <input type="checkbox"/> PHASE IV RELATED        |  |  |

**REVIEW ACTION**

- |   |   |  |
|---|---|--|
| <input type="checkbox"/> NAI (No action indicated)  | <input type="checkbox"/> Oral communication with<br>Name: [     ]   | <input checked="" type="checkbox"/> Formal Review/Memo (attached)  |
| <input type="checkbox"/> E-mail comments to:<br><input type="checkbox"/> Medical <input type="checkbox"/> Chemist <input type="checkbox"/> Pharm-Tox<br><input type="checkbox"/> Micro <input type="checkbox"/> Pharmacometrics <input type="checkbox"/> Others<br>(Check as appropriate and attach e-mail) | <input type="checkbox"/> Comments communicated in<br>meeting/Telecon. see meeting minutes<br>dated: [     ] | <input checked="" type="checkbox"/> See comments below<br><input type="checkbox"/> See submission cover letter<br><input checked="" type="checkbox"/> OTHER (SPECIFY BELOW):<br>[consult review] |

The consultation questions from Division of Antiviral Products (DAVP):

Question 1) Is the increase in the systemic exposure of norelgestromin (NGMN), when Ortho Tri-cyclen Lo is co-administered with QUAD, clinically relevant?

Response: Co-administration of QUAD with Ortho Tri-Cyclen Lo is not expected to compromise the contraception efficacy in that progestin component of the pill usually plays a more important role than the estrogen component. For the safety impact, we did not find evidence to either support or against the safety of long-term use of Tri-Cyclen Lo when NGMN exposure is markedly increased.

**Reviewer's comments:**

When Ortho Tri-Cyclen Lo was taken with QUAD, mean  $C_{max}$ ,  $C_{tau}$ , and  $AUC_{tau}$  of NGMN (active metabolite of norgestimate/NGM) were increased by 108 %, 167 %, and 126 %, compared to those when Ortho Tri-Cyclen Lo was taken alone, respectively. The kinetics of NGMN are dose proportional following NGM doses of 0.18 to 0.25 mg (source: NDA 021241, Ortho Tri-Cyclen Lo label). However, it is not known about the dose proportionality beyond 0.25 mg. We searched clinical studies or individual research investigations looking into the safety of

NGM at doses higher than 0.25 mg.

- 1) NGM containing products: NGM 0.25 mg is the highest strength approved in the United States.
  - Ortho Tri-Cyclen Lo (NDA 021241, approval on August 22, 2002) is a triphasic oral contraceptive (OC) containing 0.025 mg of EE and varying amounts of NGM, from 0.18 mg NGM in the 1st week of treatment, and rising to 0.25 mg NGM in the 3rd week of active treatment.
  - Ortho Cyclen-21 is the first NGM containing OC approved in the United States (NDA 019653, approval on December 29, 1989). Ortho Cyclen-21 consists of 0.25 mg of NGM and 0.035 mg of EE containing tablet to be taken once daily for 21 days followed by 7-days placebo for each menstrual cycle.
  - Ortho Cyclen-21 has about 16% higher NGM dose than Ortho Tri-Cyclen Lo per menstrual cycle (i.e., 28 days), but this magnitude of increase in NGM is still far less than that observed in the DDI study, i.e. more than 100% increase.
  
- 2) NGMN containing product:
  - Ortho Evra (NDA 021180, approval on November 20, 2001) is a combination transdermal contraceptive patch, containing 6.00 mg NGMN and 0.75 mg EE.
  - In Ortho Evra product label, the PK profiles of NGMN following administration of an oral contraceptive (containing NGM 0.25 mg / EE 0.035 mg) was compared to the 7-day transdermal ORTHO EVRA patch during cycle 2 in 32 healthy female volunteers. The mean PK profiles were different between the two products in that transdermal patch has higher steady state concentrations (C<sub>ss</sub>) and lower peak concentrations. Therefore, the safety profile of Ortho Evra may not be extrapolated to that of OC products such as Ortho Cyclen, Ortho Tri-Cyclen, and Ortho Tri-Cyclen Lo.
  
- 3) Clinical study data: 0.25 mg NGM is the highest strength studied in NDAs of Ortho Cyclen-21, Ortho Tri-Cyclen, and Ortho Tri-Cyclen Lo.
  - During the clinical development of Ortho Cyclen-21, the optimal dose range of NGM was determined by assessing 9 OC regimens with the highest tested strength of 0.25 mg NGM.
  - Subsequent NDAs containing NGM, i.e., Ortho Tri-Cyclen, and Ortho Tri-Cyclen Lo, have not studied doses higher than 0.25 mg NGM. Therefore, there is no information available as to why 0.25 mg NGM was selected. In addition, there is no information about the safety of NGM doses higher than 0.25 mg.
  
- 4) Literature search:
  - We performed a literature review. To our knowledge, there are no clinical studies conducted with NGM dose higher than 0.25 mg.
  - In addition, no post-marketing studies are available to indicate that more than 2-fold increase of NGMN exposure from 0.25 mg is safe.
  
- 5) Food effect
  - Food can increase the systemic exposure of some progestins, which lead to certain level of variation in the progestin exposure when the OC is taken with meal. If this is true for Ortho Tri-Cyclen Lo (or Ortho Tri-Cyclen, Ortho Cyclen), then the clinical phase 3 or post-marketing data may be used to support the safety of Ortho Tri-Cyclen Lo when the NGMN exposure is increased. This is due to the fact the phase 3 studies of Ortho Tri-Cyclen Lo (or Ortho Tri-Cyclen, Ortho Cyclen) were conducted without regard to meals. However, the food

effect study (#ESTNRG-PHI-004, Ortho-Prefest, NDA 21040) indicated that high fat meal did not affect NGMN AUC but decreased the Cmax of NGMN by 16%.

Question 2) If QUAD and Ortho Tri-cyclen Lo cannot be co-administered, are there other options for oral contraceptive use that may be safer than Ortho Tri-cyclen Lo?

Response: We do not believe that the results of current DDI study can be extrapolated to other COC containing different progestins. Therefore, we recommend that alternative contraceptive method such as non-hormonal contraceptive or intrauterine device (IUD) containing levonorgestrel or copper should be considered.

**Reviewer's Comments:**

- Hormonal contraceptive products such as transdermal patch or implant: Co-administration of QUAD may affect the systemic exposure of progestin and thus affecting the safety or efficacy of the contraceptives. However, there were no such DDI studies performed with QUAD.

**Labeling Recommendation:**

- The Clinical Pharmacology Team recommends against (b) (4)  
(b) (4)
- QUAD label should include the description of PK changes of Ortho Tri-Cyclen Lo when taken with QUAD.
- It should be stated in the label that DDI study of QUAD with COCs containing different progestins were not studied. Alternative contraceptive method such as non-hormonal contraceptives or IUDs containing levonorgestrel or copper should be considered.

**BACKGROUND:**

Division of Reproductive and Urologic Products (DRUP) has received a consult from DAVP for the drug interaction study between an oral contraceptive and a new antiviral drug (QUAD, NDA 203100, submitted on October 27, 2011) containing elvitegravir /cobicistat/ emtricitabine/ tenofovir disoproxil fumarate (EVG/COBI/FTC/TDF) on March 23, 2012. The applicant assessed the effect of QUAD on the PK of the individual components of an oral contraceptive, Ortho Tri-Cyclen Lo, in trial GS-US-236-0106. The results of the trial showed that mean Cmax, Ctau, and AUCtau of major active metabolite of NGM, NGMN, were increased by 108 %, 167 %, and 126 %, while the mean Ctau and AUCtau of EE were decreased by 43 % and 25 %, after co-administration of Ortho Tri-Cyclen Lo and QUAD as compared with when Ortho Tri-Cyclen Lo was given alone. EE Cmax values were similar with or without coadministration of QUAD

**Study Rationale:**

- QUAD:
  - EVG is a weak CYP3A4 inducer
  - COBI: is a potent mechanism-based inhibitor of CYP3A4
  - The overall potential effect of QUAD on concomitant drugs is that it may inhibit CYP3A4 activity and lead to higher exposure for CYP3A4 substrate
- NGM: rapidly converts to active metabolite NGMN via esterase in the gut and liver
- NGMN: metabolism is not well characterized, with some literature evidence suggesting the involvement of UGT1A1 or CYP3A4 or both
- EE:
  - Sulfate conjugation in the gut
  - UGT1A1 glucuronidation
  - CYP3A4 hydroxylation

**Study Design:**3-Cycle OC DDI Study with QUAD Including a Lead-in Cycle (**Table 1**)**Table 1 DDI study schema**

Menstrual Cycle	Part A		Part B				
	Menstrual Cycle 1 (Lead-in)		Menstrual Cycle 1		Menstrual Cycle 2		
Study Day	L1-L21	L22-L28	1-21	22-28	29-39	40-49	50-56
Cycle Day	1-21	22-28	1-21	22-28	1-11	12-21	22-28
Norgestimate/ Ethinyl Estradiol	X (Active)	X (Inert)	X (Active)	X (Inert)	X (Active)	X (Active)	X (Inert)
EVG/COBI/ FTC/TDF	-	-	-	-	-	X	-

- Study subjects:
  - 18 healthy pre-menopausal women aged between 18-45 years old with body mass index (BMI) between 19-30 kg/m<sup>2</sup>
- Treatment Drugs
  - EVG/COBI/FTC/TDF: Part B: Menstrual Cycle 2: 10 days of daily dosing
  - Ortho Tri-Cyclen Lo (NGM: 0.180 mg/0.215 mg/0.250 mg/EE 0.025 mg)
    - Part A (if required): 28 days (21 with active drug);
    - Part B: Menstrual Cycle 1: 28 days (21 with active drug) + Menstrual Cycle 2: 28 days (21 with active drug)
- Blood sampling for PK assessment
  - Day 21 of each menstrual cycles in Part B: predose and up to 24 hours postdose
  - Analytes
    - NGMN ( norelgestromin, primary and active metabolite of NGM)
    - EE
    - FTC
    - TFV
- Blood sampling for PD assessment
  - Day 0 (baseline) and Day 21 of each menstrual cycles in Part B
  - Analytes: P, FSH and LH

**Study Results:**

- PK Parameters (**Table 2**):
  - Mean C<sub>max</sub>, C<sub>tau</sub>, and AUC<sub>tau</sub> of NGMN increased by 108 %, 167 %, and 126 %, after co-administration of NGM/EE and QUAD as compared with when NGM/EE was given alone.
  - The mean C<sub>tau</sub> and AUC<sub>tau</sub> of EE decreased by 43 % and 25 % after co-administration of QUAD. EE, while EE C<sub>max</sub> values were similar with or without coadministration of QUAD.
  - EVG and COBI exposures achieved in this study were within the range of values observed in previous clinical studies.
- PD Parameters (FSH, LH, P):
  - Comparison of Day 0 to Day 21 changes in PD parameters after administration of NGM/EE + EVG/COBI/FTC/TDF vs. NGM/EE revealed a similar decrease in FSH after both treatments, but a greater decrease in LH after QUAD and NGM/EE given together than after NGM/EE alone.
  - No changes in serum progesterone were observed.

**Table 2 Summary of NGMN and EE steady-state PK parameters by treatment**

NGMN PK Parameter	Mean (%CV)		Geometric Least-squares Means Ratios (Test/Reference) (%)	90% Confidence Intervals
	NGM/EE Reference (N=15)	NGM/EE + EVG/COBI/FTC/TDF Test (N=15)		
AUC <sub>0-24</sub> (h·pg/mL)	21367.27 (17.1)	48339.22 (17.7)	225.96	(215.13, 237.34)
C <sub>0-24</sub> (pg/mL)	510.3 (23.1)	1368.2 (24.7)	266.57	(243.06, 292.35)
C <sub>max</sub> (pg/mL)	2147.0 (15.4)	4461.1 (14.5)	207.98	(199.74, 216.57)
<b>EE PK Parameter</b>				
AUC <sub>0-24</sub> (h·pg/mL)	1050.562 (32.1)	775.036 (26.1)	74.97	(69.41, 80.98)
C <sub>0-24</sub> (pg/mL)	25.8 (78.9)	13.7 (57.8)	56.48	(51.88, 61.49)
C <sub>max</sub> (pg/mL)	105.7 (30.7)	98.6 (27.8)	94.09	(85.54, 103.50)
<b>EVG PK Parameter</b>				
AUC <sub>0-24</sub> (h·ng/mL)	–	26917.65 (23.9)	–	–
C <sub>0-24</sub> (ng/mL)	–	414.8 (40.5)	–	–
C <sub>max</sub> (ng/mL)	–	2695.1 (23.7)	–	–
<b>COBI PK Parameter</b>				
AUC <sub>0-24</sub> (h·ng/mL)	–	10715.73 (29.5)	–	–
C <sub>0-24</sub> (ng/mL)	–	25.6 (74.2)	–	–
C <sub>max</sub> (ng/mL)	–	1560.3 (19.7)	–	–

**Reviewer’s Notes:**

- Of the four components in QUAD, TDF (VIREAD, NDA 021356) and FTC (EMTRIVA, NDA 021500) are approved by FDA as a single agent product and as a combination product.
- DDI of TDF with Ortho Tri-Cyclen: Per VIREAD label, there are lack of clinically significant drug interactions between TDF and Ortho Tri-Cyclen.
  - No changes in systemic exposure of EE and NGMN when coadministered with TDF
  - steady state TDF PK were similar to those observed in previous trials

SIGNATURE OF REVIEWER: Li, Li, Ph.D. \_\_\_\_\_

Date \_\_\_\_\_

SIGNATURE OF TEAM LEADER:

Date \_\_\_\_\_

Myong Jin Kim, Pharm.D.

CC.: HFD # [580]

PROJECT MANAGER: \_\_\_\_\_

Date: \_\_\_\_\_

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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LI LI  
04/09/2012

MYONG JIN KIM  
04/09/2012



# Memorandum

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH  
DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS

**Date:** March 26, 2012

**From:** Shona S. Pendse, MD, MMSc  
Medical Officer - Clinical Reviewer  
Division of Cardiovascular and Renal Products/OND/CDER

**Through:** Norman Stockbridge, MD, PhD  
Director  
Division of Cardiovascular and Renal Products/OND/CDER

**To:** Stacey Min  
Regulatory Project Manager  
Office of Antimicrobial Products/Division of Antiviral Products

**Subject:** Consult to review the renal safety of a single tablet regimen of elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate

This memo is in response to your consult to us requesting that we review the renal safety of elvitegravir 150mg/cobicistat 150mg/emtricitabine 200mg/tenofovir disoproxil fumarate 300mg or QUAD.

We received and reviewed the following materials:

1. Your consult to us dated January 18, 2012
2. Applicant's submission for NDA 203,100, dated October 24, 2011
3. Applicant's response to FDA questions about renal adverse events, dated January 8, 2012
4. Applicant's Safety Update and narratives of deaths, serious adverse events, and other adverse events, dated January 30, 2012
5. Draft review of Adam Sherwat, Medical Officer, dated February 17, 2012
6. Presentation from pharmacovigilance group on nephrotoxicity issues related to tenofovir
7. Multiple references on tenofovir nephrotoxicity and HIV-associated chronic kidney disease

## Background

Quad is a new four-drug, fixed-dose, combination product with a proposed indication of complete treatment of HIV-1 infection in anti-retroviral treatment naïve adults. This combination product consists of two approved agents, emtricitabine (FTC, Emtriva®) and tenofovir disoproxil fumarate (TDF, Viread®), which constitute a standard of care dual nucleoside/nucleotide reverse transcriptase inhibitor backbone (FTC/TDF, TVD, Truvada®) and two new chemical entities, elvitegravir (EVG) and cobicistat (COBI).

Elvitegravir (EVG) belongs to the new class of HIV-1 integrase strand-transfer inhibitors (INSTIs) that prevent integration of HIV-1 genetic material into the host-cell genome. Cobicistat (COBI) is a new chemical entity and structural analogue of ritonavir without antiretroviral activity. It is a cytochrome P450 3A (CYP3A) inhibitor which is being used as a booster to enhance the exposure of CYP3A substrates, including elvitegravir.

Of the QUAD components, tenofovir has known renal toxicity, resulting primarily in a proximal tubulopathy, but emtricitabine does not. In the Phase 3 trials of QUAD, there was a higher incidence of increased serum creatinine as well as proteinuria in the QUAD group compared to either of the control arms, both of which included tenofovir. There were also more discontinuations secondary to renal adverse events (AEs) such as renal failure, Fanconi's syndrome, and increased blood creatinine in the QUAD group than in either of the comparator groups. Many of these cases appeared to be consistent with proximal renal tubular dysfunction. Thus, we have been asked to provide input related to the renal safety of QUAD.

## Tenofovir Nephrotoxicity

Tenofovir, one of the four components of the QUAD, is structurally similar to the acyclic nucleotide analogs adefovir and cidofovir, both of which have been found to be nephrotoxic. These two drugs cause proximal tubulopathies as a result of acute tubular necrosis (ATN) and Fanconi's syndrome<sup>12</sup>. The underlying mechanism is via disruption of proximal tubular mitochondrial function, by inhibiting mitochondrial DNA polymerase- $\gamma$ , which is the only enzyme that replicates mitochondrial DNA. As a result, mitochondrial DNA is depleted, ultimately resulting in decrease in adenosine triphosphate production, impaired cell function, and cell injury and/or death.

Early randomized clinical trials and post-marketing data of tenofovir in relative healthy HIV-positive subjects failed to show evidence of nephrotoxicity. Since the inclusion of tenofovir into clinical practice, however, reports of nephrotoxicity, including toxic ATN, Fanconi's syndrome, and rare cases of nephrogenic diabetes insipidus, have emerged. Renal histopathology reveals acute tubular injury primarily in the proximal tubules.

The development of nephrotoxicity with tenofovir has been found to occur with as little as a few months<sup>3</sup> of tenofovir therapy but can also occur after many years of therapy. Herlitz and colleagues collected a case series of patients with tenofovir nephrotoxicity, and they reported a

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<sup>1</sup> Perazella, Tenofovir-induced kidney disease: an acquired renal tubular mitochondriopathy. *Kidney International* (2010). 78: 1060-1063.

<sup>2</sup> Tanji et al. Adefovir nephrotoxicity: possible role of mitochondrial DNA depletion. *Hum Pathol* (2011). 32: 734-740.

<sup>3</sup> Fernandez-Fernandez et al. Tenofovir Nephrotoxicity: 2011 Update. *AIDS Research and Treatment* (2011). 2011: article ID 354908.

median duration of therapy of 8 months<sup>4</sup>. Another case series by Izzedine et al reported proximal tubulopathy after 6-7 months of therapy with tenofovir<sup>5</sup>.

Risk factors that have been suggested for tenofovir-associated nephrotoxicity include advanced age, lower body weight, concomitant nephrotoxic therapies, advanced HIV infection, and ritonavir-boosted protease inhibitor regimens.

The current labeling for both emtricitabine and tenofovir recommend calculation of creatinine clearance prior to and during therapy. Due to the renal clearance of both drugs, the labeling also recommends decrease in the dosing-interval in the setting of renal impairment. In addition, the labeling for tenofovir notes renal dysfunction, acute tubular necrosis, Fanconi's syndrome, proximal renal tubulopathy, interstitial nephritis, increased creatinine, proteinuria, nephrogenic diabetes insipidus, and polyuria as possible adverse reactions.

The HIV Medicine Association of the Infectious Diseases Society of America recommends that patients receiving tenofovir who have a GFR <90 mL/min per 1.73 m<sup>2</sup> or patients receiving ritonavir-boosted protease inhibitor regimens should be monitored at least biannually for measurements of renal function, serum phosphorus, and urine analysis for proteinuria and glycosuria.<sup>6</sup> Other experts recommend more frequent monitoring, such as every 3 months<sup>7</sup>.

### **Sources of Safety Data**

Sources of safety data include two Phase 3 trials, GS-US-236-0102 (referred in this review as 0102) and GS-US-236-0103 (referred to in this review as 0103), which together constitute the primary safety database. The applicant also included another Phase 2 trial in their primary pooled safety database, GS-US-236-0104 (referred as 0104), which has been included as supportive data for some of the analyses in this review as well. Additional sources of data for this review include a Phase 3 Study, GS-US-216-0114 (referred as 0114), which the applicant provided as part of a safety update, and a second study which was used to evaluate the effect of cobicistat and ritonavir on renal function, study GS-US-216-0121 (referred as 0121). Please refer to Figure 1 and Figure 2 below for trial schema for trials 0102 and 0103.

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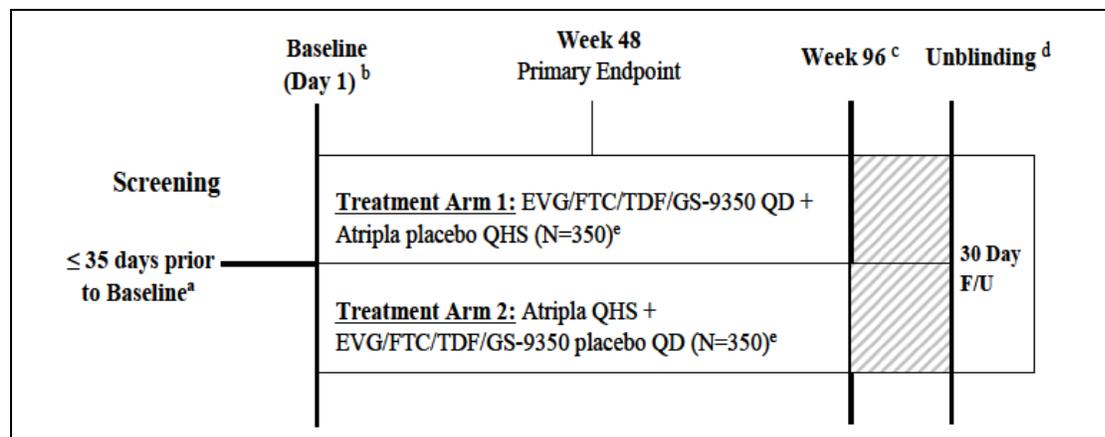
<sup>4</sup> Herlitz LC et al. Tenofovir nephrotoxicity: acute tubular necrosis with distinctive clinical, pathological, and mitochondrial abnormalities. *Kidney International* (2010). 78: 1171-1177.

<sup>5</sup> Izzedine et al. Renal safety of tenofovir in HIV treatment-experienced patients. *AIDS* (2004). 18(7): 1074-1076.

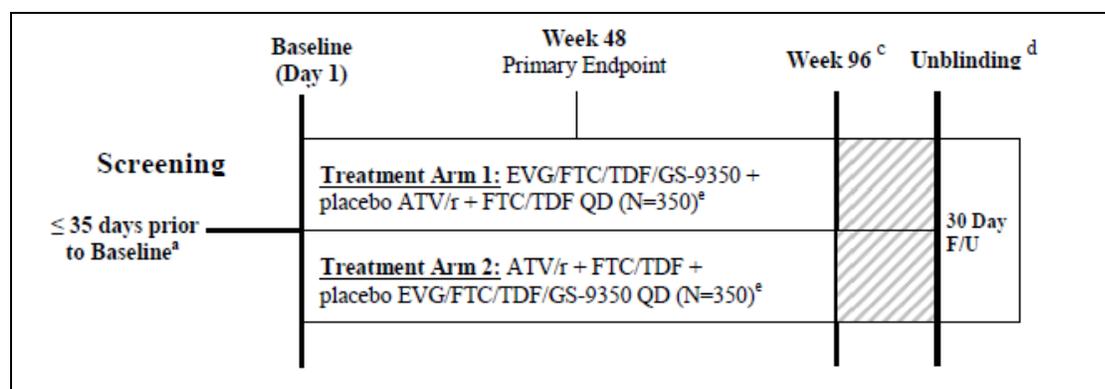
<sup>6</sup> Gupta SK et al. Guidelines for the management of chronic kidney disease in HIV-infected patients: recommendations of the HIV Medicine Association of the Infectious Diseases Society of America. *CID* (2005). 40(11): 1559-1585

<sup>7</sup> Fine DM et al. Renal disease in patients with HIV infection, epidemiology, pathogenesis, and management. *Drugs* (2008). 68(7): 963-980.

**Figure 1: Study Schema for Trial 0102**



**Figure 2: Study Schema for Trial 0103**



The active comparators for the two Phase 3 trials are efavirenz/emtricitabine/tenofovir (Atripla®) for trial 0102 and ritonavir-boosted atazanavir + emtricitabine + tenofovir for trial 0103. Thus, both of the active comparators included tenofovir and emtricitabine, and differed with regard to efavirenz vs. ritonavir-boosted atazanavir. Of particular importance is the fact that neither efavirenz nor atazanavir have been associated with proximal tubular toxicity.<sup>89</sup>

Entry criteria for trials 0102 and 0103 included eGFR by Cockcroft-Gault  $\geq 70$  ml/min, and neither of the trials had eligibility criteria related to proteinuria or glycosuria.

The duration of the double-blind treatment period for the Phase 3 trials was 96 weeks, and upon the completion of this period, subjects continued to take their blinded study drug and attend visits every 12 weeks until treatment assignments had been unblinded. At the unblinding visit for both trials, subjects were given the option to participate in an open-label rollover extension study. For these two trials, results of the first 48 weeks of blinded treatment were submitted as part of this application.

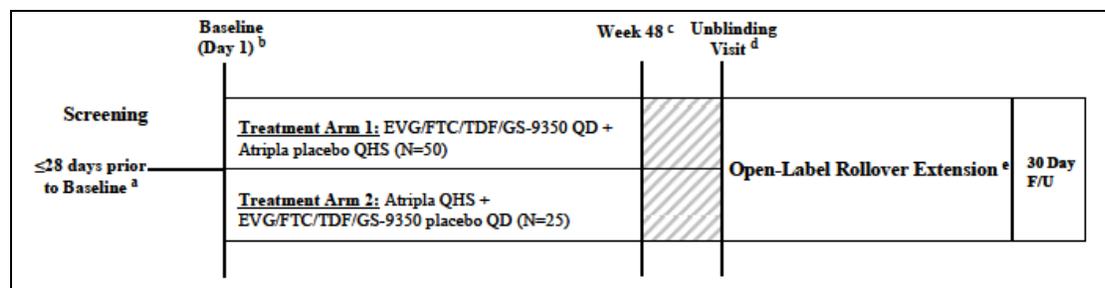
Both trials followed eGFR by Cockcroft-Gault along with urinalysis and phosphorous. These elements were collected at baseline, at weeks 2, 4, 8, 12, 16, 24, 32, 40, and 48, and then every 12 weeks thereafter until the unblinding visit. In addition, subjects were asked about AE's at all visits and renal events were evaluated as pre-specified adverse events of interest.

<sup>8</sup> Barbour TD et al. Efavirenz-associated podocyte damage. AIDS (2007 Jan). 21(2): 257-8.

<sup>9</sup> Chan-Tack KM et al. Atazanavir-associated nephrolithiasis: cases from the US Food and Drug Administration's Adverse Event Reporting System. AIDS (2007 May). 21(9): 1215-8.

As mentioned earlier, another trial, 0104, was used for supportive data. Trial 0104 is a Phase 2, randomized, double-blind, double-dummy, multi-center, randomized, active-controlled study to assess the safety and efficacy of the QUAD STR versus the active comparator efavirenz/emtricitabine/tenofovir (Atripla®) in HIV-1 infected, antiretroviral treatment-naive adult subjects. The trial duration was 60 weeks for the randomized, double-blind period. Eligibility for the study included eGFR by Cockcroft-Gault  $\geq 70$  ml/min and as in the other trials had no eligibility criteria for either proteinuria or glycosuria. As in the prior two trials, trial 0104 followed eGFR by Cockcroft-Gault along with urinalysis, phosphorous, and adverse events at all visits. Please refer to Figure 3 for the study schema for trial 0104.

**Figure 3: Study Schema for Trial 0104**



The final two trials, trial 0114 and 0121, were used as additional sources of safety data in this review. Trial 0114 is an ongoing Phase 3, randomized, double-blind, multi-center, multiple dose, active-controlled study in HIV-1 infected treatment naïve subjects which was designed to evaluate the safety and efficacy of TVD + ATV boosted with COBI (ATV/co) versus TVD + ATV boosted with RTV. Thus, one arm was treated with atazanavir boosted with cobicistat and the other with atazanavir boosted with ritonavir, in addition to therapy with emtricitabine and tenofovir in both arms. A total of 692 subjects received at least one dose of study drug (ATV/co + TVD 344, ATV/r + TVD 348).

Trial 0121 is a Phase 1 randomized, blinded placebo-controlled study designed to evaluate the effect of cobicistat and ritonavir on renal function as assessed by markers of GFR. This study had two cohorts of subjects, the first comprised of 36 healthy subjects with estimated GFR by Cockcroft-Gault ( $eGFR_{CG}$ )  $\geq 80$  mL/min, and the second comprised of 18 subjects with stable mild to moderate renal impairment ( $eGFR_{CG}$  50-79 mL/min). The subjects in cohort 1 were randomized, in a double dummy fashion, to receive either cobicistat 150 mg or ritonavir 100 mg once daily for seven days, while for cohort 2, subjects received only cobicistat 150mg in an open-label fashion for seven days. Renal function was assessed on Days 0 (baseline), 7, and 14 in subjects in Cohorts 1 and 2 using the Cockcroft-Gault method ( $eGFR_{CG}$ ), estimated GFR by MDRD ( $eGFR_{MDRD}$ ), direct measurement using iohexol clearance, GFR based on cystatin C clearance, and measurement of 24-hour urinary creatinine excretion ( $CrCl_{24h}$ ).

### Baseline Demographics

Across trials 0102, 0103, and 0104, the baseline demographic characteristics appeared to be well-balanced between the QUAD, ATR, and ATV/r + TVD treatment arms. Mean (SD) baseline estimated glomerular filtration rate (GFR) calculated using the Cockcroft-Gault equation ( $eGFR_{CG}$ ) was  $120.6 \pm 32.61$  mL/min, by MDRD was  $99.8 \pm 19.93$  ml/min/ $1.73m^2$ , and by cystatin-C was  $97.5 \pm 21.38$  ml/min/ $1.73m^2$ .

## **Exposure to Drug**

A total of 749 subjects received at least one dose of QUAD in trials 0102, 0103, and 0104, with 727 subjects exposed to QUAD for at least 12 weeks, 688 subjects exposed for at least 40 weeks, 509 subjects for at least 48 weeks, and 164 subjects exposed for at least 60 weeks. For the active comparator arms, 375 subjects received ATR, and 355 subjects received ATV/r+TVD. The median duration of exposure to study drug was 48.4 weeks (Q1–Q3: 47.9–60.0) in the QUAD group, 58.9 weeks (Q1–Q3: 48.1–60.1) in the ATR group, and 48.1 weeks (Q1–Q3: 46.1–51.0) in the ATV/r+TVD group.

## **Treatment-Emergent Renal Adverse Events in the Phase 3 Trials**

Selected treatment-emergent renal adverse events in the Phase 3 trials can be seen in Table 1. Subjects with multiple occurrences of the same AE were only counted once for that AE. As can be seen, the overall number of treatment-emergent events was small, but they appeared to occur at a greater incidence in the QUAD treatment arm compared to the ATR or ATV/r + TVD arms. The only exception to this was the adverse event of nephrolithiasis, which was more frequent in ATR treatment arm than the other two arms (though one would have expected nephrolithiasis to be more frequent in the atazanavir arm).

**Table 1: Selected Treatment Emergent Renal Adverse Events in the Phase 3 Trials (0102 and 0103) by MedDRA High Level Term and Preferred Term**

	<b>QUAD</b>	<b>ATR</b>	<b>ATV/r + TVD</b>
	236-0102, 0103 (N=701)	236-0102 (N=352)	236-0103 (N=355)
<b>Adverse Events, n (%)</b> (MedDRA High Level Term and Preferred Term)			
<b>Nephropathies And Tubular Disorders NEC</b>	1 (0.1%)	0 (0.0%)	1 (0.3%)
Fanconi Syndrome Acquired	1 (0.1%)	0 (0.0%)	0 (0.0%)
Nephropathy Toxic	0 (0.0%)	0 (0.0%)	1 (0.3%)
<b>Renal Failure And Impairment</b>	4 (0.6%)	1 (0.3%)	0 (0.0%)
Renal Failure	4 (0.6%)	1 (0.3%)	0 (0.0%)
<b>Renal Function Analyses</b>	7 (1.0%)	1 (0.3%)	1 (0.3%)
Blood Creatinine Increased	7 (1.0%)	1 (0.3%)	1 (0.3%)
<b>Renal Lithiasis</b>	4 (0.6%)	6 (1.7%)	3 (0.8%)
Nephrolithiasis	4 (0.6%)	6 (1.7%)	3 (0.8%)
<b>Renal Obstructive Disorders</b>	1 (0.1%)	0 (0.0%)	0 (0.0%)
Hydronephrosis	1 (0.1%)	0 (0.0%)	0 (0.0%)
<b>Urinary Abnormalities</b>	15 (2.1%)	10 (2.8%)	6 (1.7%)
Hematuria	9 (1.2%)	9 (2.6%)	4 (1.1%)
Leukocyturia	1 (0.1%)	0 (0.0%)	2 (0.6%)
Microalbuminuria	1 (0.1%)	0 (0.0%)	0 (0.0%)
Proteinuria	10 (1.4%)	3 (0.9%)	3 (0.8%)
Pyuria	1 (0.1%)	0 (0.0%)	0 (0.0%)
<b>Urinary Tract Signs And Symptoms NEC</b>	14 (2.0%)	3 (0.9%)	3 (0.8%)
Nocturia	10 (1.4%)	2 (0.6%)	1 (0.3%)
Polyuria	3 (0.4%)	0 (0.0%)	1 (0.3%)
Renal Colic	1 (0.1%)	1 (0.3%)	1 (0.3%)

### Patients with Discontinuation of QUAD due to Renal Adverse Events

In the Phase 3 trials, there were five subjects that discontinued study drug due to a renal AE in trial 0102 (all of whom were in the QUAD arm) and 2 subjects in trial 0103 (1 in QUAD and 1 in the ATV/r + TVD arm). The narratives were reviewed, and those with evidence of urinary abnormalities suggestive of tubular dysfunction were identified (below). Of these, five subjects had some evidence of proteinuria, normoglycemic glycosuria, and/or hypophosphatemia.

- Subject 0663-6049 (QUAD) developed an increase in  $S_{Cr}$  from a baseline of 1.26 mg/dL to 2.86 and 2+ proteinuria. After discontinuation of study drug,  $S_{Cr}$  decreased to 1.65 by SD 113, where it remained until the last study visit on SD 590. Fractional excretion of phosphate increased to 28.6% by SD 16 and returned to near baseline by SD 421. His

last study labs on SD 590 revealed  $S_{Cr}$  1.70 mg/dL, eGFR 55.7 mL/min, and no proteinuria.

- Subject 0663-6517 (QUAD) developed an increase in  $S_{Cr}$  from baseline of 1.04 mg/dl to a peak of 1.49 mg/dL. Creatinine ultimately returned to baseline, 0.97 mg/dL. The subject did not develop glycosuria but did have evidence of persistent trace proteinuria. His fractional excretion of phosphate peaked at 13.6% on SD 169 and returned to less than his baseline after study drug discontinuation.
- Subject 0754-6242 (QUAD) developed a rise in  $S_{Cr}$  from a baseline of 1.13 mg/dl to a peak of 1.99 mg/dL, normoglycemic 4+ glycosuria, increase in baseline proteinuria (from trace at baseline to 2+), and hypophosphatemia. Seventeen days after discontinuation of QUAD, the subject's hypophosphatemia resolved. At last assessment,  $S_{Cr}$  decreased to 1.54 mg/dL, urine glucose decreased to trace levels, and urine protein was stable at 2+.
- Subject 0698-6222 (QUAD) developed an increase in creatinine from baseline of 1.0 mg/dL to peak of 1.65 mg/dL, along with normoglycemic 1+ glycosuria and 3+ proteinuria. Fractional excretion of phosphate peaked at 29.4% and then returned to near baseline (6.4%). At last available assessment,  $S_{Cr}$  decreased to 1.31 mg/dL, and his proteinuria and glycosuria both resolved.
- Subject 2003-6267 (QUAD) developed an increase in creatinine from baseline of 1.52 mg/dL to a peak of 4.47 mg/dL, along with normoglycemic 3+ glycosuria and 2+ proteinuria. The subject also had an increase in his fraction excretion of phosphate to a peak of 73.9 %, which improved after study drug discontinuation. At the last available assessment, creatinine was 1.82 mg/dL and resolution of both glycosuria and proteinuria.

The Applicant also identified 11 subjects who discontinued study drug due to a renal cause in trial 0114. Again, the narratives were reviewed and those with evidence of tubular dysfunction were identified. Five cases in the ATV/co + TVD and 3 cases in the ATV/r + TVD had evidence of proteinuria, glycosuria and/or hypophosphatemia.

- Subject 0691-8292 (ATV/co + TVD) developed an increase in  $S_{Cr}$  from 0.77 to 0.94 mg/dL along with glycosuria, proteinuria, and hypophosphatemia. After discontinuation of study drug,  $S_{Cr}$  decreased to 0.89 mg/dL and all of the other abnormalities normalized.
- Subject 0986-8283 (ATV/co + TVD) developed an increase in  $S_{Cr}$  from 1.02 to 3.58 along with 1+ glycosuria, 2+ proteinuria, and hypophosphatemia. After discontinuation of study drug,  $S_{Cr}$  decreased to 1.93 mg/dL and all of the other abnormalities resolved.
- Subject 4127-8204 (ATV/co + TVD) developed an increase in  $S_{Cr}$  from 0.70 to 1.19 mg/dL along with 1+ glycosuria and 2+ proteinuria. After study drug discontinuation,  $S_{Cr}$  decreased to 0.98, the glycosuria resolved, and the proteinuria decreased to 1+.
- Subject 2840-8066 (ATV/co + TVD) developed an increase in  $S_{Cr}$  from 1.03 to 1.79 mg/dL along with 2+ proteinuria but there were no follow-up labs available after study drug discontinuation.
- Subject 4142-8361 (ATV/co + TVD) developed an increase in  $S_{Cr}$  from 1.06 to 5.07 along with 3+ glycosuria and 2+ proteinuria but there were numerous other comorbidities, including a history of hepatitis c and development of enterobacter sepsis and diabetes mellitus. After discontinuation of study drug,  $S_{Cr}$  decreased to 2.19 mg/dL.
- Subject 1978-8016 (ATV/r + TVD) developed an increase in  $S_{Cr}$  from 0.91 to 1.30 along with 2+ glycosuria, 2+ proteinuria, and hypophosphatemia. After study drug

discontinuation,  $S_{Cr}$  decreased to the 1.03 to 1.17 range and all other abnormalities resolved.

- Subject 3976-8058 (ATV/r + TVD) developed an increase in  $S_{Cr}$  from 1.00 to 1.59 along with 3+ glycosuria, 2+ proteinuria, and hypophosphatemia but of note was the fact that this subject also had hyperglycemia. After discontinuation of study drug,  $S_{Cr}$  decreased to the 1.48 to 1.56 range, phosphorous improved to 2.9, and glycosuria and proteinuria decreased to trace levels.
- Subject 4169-8476 (ATV/r + TVD) developed an increased in  $S_{Cr}$  from 0.86 to 1.30 along with 1+ proteinuria. After discontinuation of study drug,  $S_{Cr}$  decreased to 0.85 and proteinuria resolved.

### **Changes in creatinine, cystatin-C, proteinuria, urinary phosphate, and glycosuria**

Increase in serum creatinine and decrease in creatinine clearance were noted in the QUAD arm compared to the two active comparators. In the Phase 3 safety trials, mean creatinine increased as early as Week 2, with median increase from baseline to Week 2 of  $0.09 \pm 0.12$  mg/dL. This was larger than the changes seen in the ATR ( $0.01 \pm 0.11$  mg/dL) or ATV/r + TVD group ( $0.06 \pm 0.13$  mg/dL). For the change from baseline to Week 48, the results were  $0.14 \pm 0.13$  mg/dL (QUAD),  $0.02 \pm 0.12$  mg/dL (ATR) or  $0.09 \pm 0.13$  mg/dL (ATV/r + TVD group).

A higher percentage of subjects in the QUAD group compared with the ATR or ATV/r+TVD groups had Grade 1 serum creatinine abnormalities reported (QUAD 6.7%, 47 subjects; ATR 0.9%, 3 subjects; ATV/r+TVD 4.0%, 14 subjects); however, the incidence of Grade 2 serum creatinine abnormalities was the same in each group.

Similarly, in the Phase 3 trials, a decrease of eGFR by Cockcroft-Gault was seen in the QUAD arm ( $-10 \pm 13$  ml/min). This was larger than the change observed in the ATR ( $-2 \pm 14$  ml/min) and ATV/r + TVD ( $-5 \pm 13$  ml/min) groups. The change from baseline to Week 48 was  $-14 \pm 15$  ml/min (QUAD),  $-2 \pm 16$  ml/min (ATR) or  $-9 \pm 16$  ml/min (ATV/r + TVD group).

Cystatin C is a low molecular weight protein that is produced at a constant rate and is freely filtered by the glomerulus, reabsorbed, and catabolized, but is not secreted by the renal tubules. In contrast to the Cockcroft-Gault creatinine clearance, there was no mean decrease in cystatin C-derived creatinine clearance in these trials.

With regard to serum phosphate, there was a higher overall incidence of hypophosphatemia of any grade in the QUAD group than the ATR comparator in trial 0102 (29 subjects, or 8.3%, in the QUAD arm and 16 subjects, or 4.5%, in the ATR arm) but this was not the case in trial 0103 (17 subjects, or 4.8%, in QUAD arm, compared to 22 subjects, or 6.3% in the ATV/r + TVD arm).

Proteinuria of any grade was observed more frequently in the QUAD arm than in either of the comparator arms in both trials (144 subjects, or 41.5% of the QUAD arm versus 101 subjects, or 28.8%, of the ATR comparator arm in trial 0102; and 126 subjects, or 35.8%, of the QUAD arm versus 85 subjects, or 24.1%, of the ATV/r + TVD arm in trial 0103). Proteinuria was predominantly Grade 1 in severity. Among subjects with no protein in the urine at baseline (i.e., negative result at baseline), similar percentages of subjects in each treatment group had confirmed proteinuria (trace or worse) during study treatment.

Urine fractional excretion of phosphate was increased in both the QUAD group as well as the comparator, but mean change from baseline to week 48 was higher in the QUAD group as compared to either the ATR or ATV/r + TVD comparators: in trial 0102, mean change from

baseline was 1.0-2.3% for the QUAD group versus 0.5-1.0% for the ATR group, and in trial 0103, mean change was 2.3-2.7% for the QUAD group and 1.3-1.7% for the ATV/r + TVD group.

Glycosuria of any grade was observed in 9 subjects, or 2.6%, of the QUAD arm and in 5 subjects, or 1.4%, of the ATR comparator arm in trial 0102. In trial 0103, glycosuria was observed in fewer subjects in the QUAD arm compared to the ATV/r + TVD arm (7 subjects, or 2.0% in QUAD versus 20 subjects, or 5.7%, in the comparator). This is an underestimate, however, of the true occurrence of glycosuria since the applicant only included instances of grade 2 or higher glycosuria in these analyses.

### **COBI and change in eGFR: component of inhibition of tubular secretion of creatinine**

The applicant reasons that the elevation in creatinine and decrease in estimated creatinine clearance and estimated GFR (eGFR) seen with QUAD is due to cobicistat-related inhibition of tubular creatinine secretion rather than an actual decrease in GFR (aGFR). They suggest that the results for cysGFR in the pooled safety analysis set of Studies GS-US-236-0102, GS-US-236-0103, & GS-US-236-0104 lend support to this hypothesis, given that creatinine levels increased, as did eGFR by Cockcroft-Gault, while cystatin-based GFR did not.

To further explore this hypothesis, the applicant did another study, 0121, which was designed to evaluate the effects of cobicistat and ritonavir on various markers of renal function. Mean eGFR<sub>CG</sub> values at baseline for cohort 1 were 21.3 mL/min (cobicistat), 116.9 mL/min (ritonavir), and 113.8 mL/min (placebo), and for cohort 2, the mean eGFR<sub>CG</sub> was 68.7 mL/min.

Statistically significant ( $p < 0.05$ ) decreases were observed at Day 7 relative to Day 0 in GFR estimated using serum and/or urinary creatinine to assess renal function (eGFR<sub>CG</sub>, eGFR<sub>MDRD</sub> and CrCl<sub>24h</sub>) in subjects in both cohorts receiving COBI. These decreases were reversible and eGFR (Cohorts 1 and 2) and CrCl<sub>24h</sub> (Cohort 1) values had reverted to baseline levels at Day 14. No statistically significant changes in eGFR relative to Day 0 were observed at Day 7 in subjects who had received ritonavir or placebo, or at Day 14 in subjects who had received placebo. A statistically significant increase in eGFR was noted at Day 14 in subjects who had received ritonavir. In contrast, no statistically significant differences relative to Day 0 were observed at Day 7 or Day 14 ( $p > 0.05$ ) in iohexol-based GFR or cystatin-C-based GFR assessments. The applicant asserts that the time to onset, magnitude, and resolution of the changes in eGFR<sub>CG</sub>, eGFR<sub>MDRD</sub>, and CrCl<sub>24h</sub>, together with the absence of statistically significant changes in iohexol-based GFR and cystatin-C-based GFR, provide support for the mechanism being inhibition of proximal tubular secretion of creatinine by COBI rather than actual reduction in GFR.

### **Conclusions**

QUAD is a new four-drug, fixed-dose, combination product which consists of two approved agents, emtricitabine and tenofovir disoproxil fumarate, and two new chemical entities, elvitegravir and cobicistat. Tenofovir has been found to be nephrotoxic, resulting in proximal tubulopathies as a result of acute tubular necrosis (ATN) and Fanconi's syndrome. Emtricitabine does not have known renal toxicity. The current labeling for both emtricitabine and tenofovir recommend calculation of creatinine clearance prior to and during therapy and dosing interval adjustment for patients with creatinine clearance below 50 ml/min (due to increased drug exposures in the setting of renal impairment).

In the trials of QUAD put forth in this marketing application, there was a higher incidence of creatinine and urine protein abnormalities in the QUAD group compared to either of the control arms, all of which included tenofovir. There were also more discontinuations secondary to renal adverse events (AEs) such as renal failure, Fanconi's syndrome, and increased blood creatinine in the QUAD group than in either of the comparator groups. Thus, in light of these adverse renal findings, we have been asked to provide input related to the renal safety of QUAD.

The very first issue relates to trial design. The trials in the safety analysis set all had active comparators which included both tenofovir and emtricitabine but differed with regard to the third agent, which for two trials was efavirenz and for the third trial was ritonavir-boosted atazanavir, neither of which have been associated with proximal tubular toxicity to interfere with the safety findings. The results included in this marketing application are up to 48 to 60 weeks treatment duration, with approximately 500 subjects exposed for 48 weeks and ~160 subjects exposed for 60 weeks. Although this treatment duration should capture many of the cases, this likely will be inadequate to capture cases of late-onset toxicity.

The next question is whether or not these trials were well-designed to capture renal adverse events. From the standpoint of renal monitoring, all three trials were adequate. Estimated GFR by Cockcroft-Gault was followed longitudinally in all 3 trials in the primary safety database, along with urinalysis and serum electrolytes and phosphorous, from baseline up until week 48 and then thereafter until the unblinding visit. In addition, subjects were asked about AE's at all visits.

With regard to proteinuria, the QUAD arms had higher incidence of proteinuria than did the comparators. This is likely proteinuria of tubular origin. Moreover, these trials suggest that the increases in proteinuria were more frequent in those with proteinuria at baseline, which is mechanistically understandable since we know that those with baseline kidney disease are at a higher risk for both further renal injury, and that risk of developing tenofovir toxicity is likely increased in those with renal impairment.

If one looks at the incidence of proximal tubulopathy leading to study drug discontinuation in these trials, there is a suggestion in these trials that these cases may be greater in these trials than that seen in earlier trials of tenofovir. However, the rarity of such events makes this difficult to establish with the available data.

Along the same line of reasoning, there is a suggestion in these trials that the incidence of proximal tubulopathy may be greater with regimens containing both tenofovir and COBI. Again, however, due to the small number of cases of tubulopathy, we can only hypothesize that this could be a possibility, but this is difficult to establish with the data that are available. If this were to be the case, and there was synergistic toxicity, one possible mechanism is an interaction between the two drugs resulting in the potentiation of the effect of tenofovir, such as via inhibition of tenofovir efflux from cells (such as thought to occur with ritonavir and also in the setting of renal impairment)<sup>101112</sup>.

In addition, the data on the effect of cobicistat do suggest a mechanism of inhibition of tubular secretion of creatinine, given that the serum creatinine and eGFR by Cockcroft-Gault both decrease while cystatin-C based GFR did not. However, other explanation for the decrease in

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<sup>10</sup>Rodriguez-Novoa et al. Predictors of kidney tubular dysfunction in HIV-infected patients treated with tenofovir: A pharmacogenetic study. *Clinical Infectious Diseases* (2009). 48: 108-16.

<sup>11</sup> Kiser et al. The effect of lopinavir/ritonavir on the renal clearance of tenofovir in HIV-infected patients. *Clinical Pharmacology and Therapeutics* (2008). 83(2): 265-272.

<sup>12</sup> Winston and Shepp. The role of drug interactions and monitoring in the prevention of tenofovir-associated kidney disease. *Clinical Infectious Disease* (2006). 42(11): 1657-1658.

cystatin C could be decrease in the level of HIV infection or in the degree of inflammation with drug therapy.

Thus, there may be in fact two distinct processes at work resulting in an overall picture of renal toxicity. The first is a cobicistat-induced inhibition of creatinine secretion, which is likely the cause of the creatinine increase in the subjects who had a reversible change in  $S_{Cr}$ , in which cases the creatinine clearance normalized upon discontinuation of the study drug. The second is tenofovir-induced proximal tubular changes or Fanconi's syndrome, which is seen in those subjects who developed proteinuria, glycosuria, and/or hypophosphatemia.

It is critical to identify these cases of nephrotoxicity early in the course of their development. Past history of tenofovir nephrotoxicity suggests that a proportion of subjects are left with some level of chronic kidney disease, even upon discontinuation of study drug, but that the earlier the drug is stopped the more likely it is to have a favorable renal outcome. Thus, the labeling must attempt to guide physicians to institute regular follow-up for changes in eGFR and urinary abnormalities.

### **Responses to Questions:**

1. Do you agree with the sponsor's assertion that a modest elevation in creatinine levels and decrease in estimated creatinine clearance and estimated GFR (eGFR) is to be expected with the QUAD formulation due to cobicistat-related inhibition of tubular creatinine secretion, but that actual GFR is not affected?

I agree with the fact that there is a cobicistat-induced inhibition of creatinine secretion, which is likely the cause of the creatinine increase in the subjects who had a reversible change in  $S_{Cr}$ , in which cases the creatinine clearance normalized upon discontinuation of the study drug. However, in order to appropriately guide treating physicians, the degree of creatinine elevation with cobicistat should be more definitely established by the applicant.

2. Do you agree with our current identification of the cases of proximal tubulopathy in the pooled QUAD studies (236-0102 and 236-0103) as well as in study 216-0114?

Yes, I agree with the identification of the cases of proximal tubulopathy.

3. Do you recommend any additional screening and/or monitoring measures (e.g. monitoring of dipstick urine glucose and protein, modifying the recommended minimum CrCl at baseline prior to drug initiation)?
  - Recommend evaluation of urine protein and glucose at baseline and at regular intervals (I would suggest 3-4 month intervals) during therapy with QUAD would be useful in detecting early development of tubular toxicity.
  - Recommend serum creatinine and creatinine clearance measurement both at baseline and at regular intervals (I would suggest 3-4 month intervals) during therapy with QUAD.
  - I would suggest that this enhanced level of monitoring be considered for tenofovir monotherapy as well, since we know that even monotherapy is associated with renal toxicity, and it is difficult to conclude that the toxicity seen in these trials of QUAD is any different from that seen with monotherapy.
  - With regard to modification of the minimum baseline CrCl for drug initiation, this may be reasonable to consider, not for reasons associated with the renal toxicity, but due to the fact that tenofovir exposures are approximately 25% greater when

given as part of the QUAD formulation, compared to monotherapy, and the fact that tenofovir is primarily excreted by the kidneys.

- Consider instituting enhanced pharmacovigilance to identify risk factors for development of proximal tubulopathy.
4. Do you recommend providing specific guidance in the label with respect to the level of increased serum creatinine and/or decreased calculated creatinine clearance that may indicate the presence of genuine renal dysfunction in patients treated with QUAD. Per sponsor, due to COBI's effect on creatinine secretion, some degree of serum creatinine elevation and decrease in calculated creatinine clearance is to be anticipated with the use of QUAD.

Would consider adding a statement such as: "Increases in creatinine levels (approximately .... mg/dL) following initiation of treatment with QUAD have been shown to be a result of inhibition of the tubular secretion of creatinine..."

(However, the applicant will need to provide data from cobicistat monotherapy which will allow us to more definitively establish the degree of elevation in creatinine)

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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SHONA S PENDSE  
03/26/2012

NORMAN L STOCKBRIDGE  
03/26/2012

## RPM FILING REVIEW

(Including Memo of Filing Meeting)

**To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data)]**

Application Information		
NDA # 203100 BLA#	NDA Supplement #:S- 0000 BLA STN #	Efficacy Supplement Type SE- n/a
Proprietary Name: Undetermined Established/Proper Name: Elvitegravir/Cobicistat/Emtricitabine/Tenofovir Disoproxil Fumarate (EVG/COBI/FTC/TDF) 150/150/200/300 mg Single Tablet Regimen (STR) Dosage Form: Single Tablet Regimen (STR) Strengths: 150/150/200/300 mg		
Applicant: Gilead Sciences, Inc. Agent for Applicant (if applicable): Christophe Beraud, Ph.D., Associate Director, Regulatory Affairs		
Date of Application: October 26, 2011 Date of Receipt: October 27, 2011 Date clock started after UN:		
PDUFA Goal Date: August 27, 2012		Action Goal Date (if different):
Filing Date: December 23, 2011		Date of Filing Meeting: December 16, 2011
Chemical Classification: (1,2,3 etc.) (original NDAs only) 1, 4 (NME and New Combination)		
Proposed indication(s)/Proposed change(s): Treatment of HIV-1 Infection in Treatment-Naïve Adults.		
Type of Original NDA: AND (if applicable) Type of NDA Supplement:		<input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)
<i>If 505(b)(2): Draft the "505(b)(2) Assessment" form found at: <a href="http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499">http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499</a> and refer to Appendix A for further information.</i>		
Review Classification:  <i>If the application includes a complete response to pediatric WR, review classification is Priority.</i>  <i>If a tropical disease priority review voucher was submitted, review classification is Priority.</i>		<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority  <input type="checkbox"/> Tropical Disease Priority Review Voucher submitted
Resubmission after withdrawal? <input type="checkbox"/>		Resubmission after refuse to file? <input type="checkbox"/>
Part 3 Combination Product? <input type="checkbox"/>  <i>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</i>		<input type="checkbox"/> Convenience kit/Co-package <input type="checkbox"/> Pre-filled drug delivery device/system <input type="checkbox"/> Pre-filled biologic delivery device/system <input type="checkbox"/> Device coated/impregnated/combined with drug <input type="checkbox"/> Device coated/impregnated/combined with biologic <input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Separate products requiring cross-labeling <input type="checkbox"/> Possible combination based on cross-labeling of separate products <input type="checkbox"/> Other (drug/device/biological product)

<input checked="" type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review <input type="checkbox"/> Orphan Designation  <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC  Other:	<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)			
Collaborative Review Division (if OTC product):				
List referenced IND Number(s): Elvitegravir: IND (b)(4), DMF (b)(4); Cobicistat: IND (b)(4), DMF (b)(4); Emtricitabine: IND 53,971, NDA 21-500, NDA 210896; Tenofovir DF: IND 52,849, NDA 21-356, NDA 22-577; Emtricitabine/Tenofovir DF: IND 67,671 and NDA 21-752				
Goal Dates/Product Names/Classification Properties	YES	NO	NA	Comment
PDUFA and Action Goal dates correct in tracking system?  <i>If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	X			
Are the proprietary, established/proper, and applicant names correct in tracking system?  <i>If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.</i>	X			
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug)? <i>For NDAs/NDA supplements, check the Application and Supplement Notification Checklists for a list of all classifications/properties at: <a href="http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163970.htm">http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163970.htm</a></i>  <i>If no, ask the document room staff to make the appropriate entries.</i>	X			
Application Integrity Policy	YES	NO	NA	Comment
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at: <a href="http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm">http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</a></i>		X		
<i>If yes, explain in comment column.</i>			X	
<i>If affected by AIP, has OC/DMPQ been notified of the submission? If yes, date notified:</i>			X	
User Fees	YES	NO	NA	Comment
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	X			

<p><u>User Fee Status</u></p> <p><i>If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.</i></p>	<p>Payment for this application:</p> <p><input checked="" type="checkbox"/> Paid  <input type="checkbox"/> Exempt (orphan, government)  <input type="checkbox"/> Waived (e.g., small business, public health)  <input type="checkbox"/> Not required</p>																			
<p><i>If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.</i></p>	<p>Payment of other user fees:</p> <p><input checked="" type="checkbox"/> Not in arrears  <input type="checkbox"/> In arrears</p>																			
<p><b>505(b)(2)</b>  <b>(NDAs/NDA Efficacy Supplements only)</b></p>	<p><b>YES</b></p>	<p><b>NO</b></p>	<p><b>NA</b></p>	<p><b>Comment</b></p>																
<p>Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?</p>			<p>X</p>																	
<p>Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? [see 21 CFR 314.54(b)(1)].</p>			<p>X</p>																	
<p>Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug [see 21 CFR 314.54(b)(2)]?</p> <p><i>If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the (b)(2) review staff in the Immediate Office of New Drugs</i></p>			<p>X</p>																	
<p>Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan or pediatric exclusivity)?  Check the <i>Electronic Orange Book</i> at:  <a href="http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm">http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm</a></p> <p><b>If yes, please list below:</b></p> <table border="1" data-bbox="203 1446 1349 1587"> <thead> <tr> <th>Application No.</th> <th>Drug Name</th> <th>Exclusivity Code</th> <th>Exclusivity Expiration</th> </tr> </thead> <tbody> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> </tbody> </table>	Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration															<p>X</p>	
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration																	
<p><i>If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 108(b)(2). Unexpired, 3-year exclusivity will only block the approval, not the submission of a 505(b)(2) application.</i></p>	<p><b>YES</b></p>	<p><b>NO</b></p>	<p><b>NA</b></p>	<p><b>Comment</b></p>																
<p>Does another product (same active moiety) have orphan exclusivity for the same indication? <i>Check the Orphan Drug Designations and Approvals list at:</i>  <a href="http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm">http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm</a></p>	<p>X</p>			<p>Viread (tenofovir) was approved for orphan designation on March 17, 2009</p>																

				for treatment of pediatric HIV infection.
<p><b>If another product has orphan exclusivity</b>, is the product considered to be the same product according to the orphan drug definition of sameness [see 21 CFR 316.3(b)(13)]?</p> <p><i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy</i></p>		X		
<p>Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? (<i>NDAs/NDA efficacy supplements only</i>)</p> <p>(b) (5)</p> <p><i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i></p>	(b) (5)			
<p>Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (<i>NDAs only</i>)?</p>		X		
<p><b>If yes</b>, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)?</p> <p><i>If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.</i></p>				

Format and Content				
<p><i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i></p>	<input type="checkbox"/> All paper (except for COL) <input checked="" type="checkbox"/> All electronic <input type="checkbox"/> Mixed (paper/electronic)  <input checked="" type="checkbox"/> CTD <input type="checkbox"/> Non-CTD <input type="checkbox"/> Mixed (CTD/non-CTD)			
<p><b>If mixed (paper/electronic) submission</b>, which parts of the application are submitted in electronic format?</p>				
Overall Format/Content	YES	NO	NA	Comment
<p><b>If electronic submission</b>, does it follow the eCTD guidance?<sup>1</sup>  <b>If not</b>, explain (e.g., waiver granted).</p>	X			
<p><b>Index:</b> Does the submission contain an accurate comprehensive index?</p>	X			
<p>Is the submission complete as required under 21 CFR 314.50</p>	X			

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<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf>

(NDAs/NDA efficacy supplements) or under 21 CFR 601.2 (BLAs/BLA efficacy supplements) including:  <input checked="" type="checkbox"/> legible <input checked="" type="checkbox"/> English (or translated into English) <input checked="" type="checkbox"/> pagination <input checked="" type="checkbox"/> navigable hyperlinks (electronic submissions only)  <b>If no, explain.</b>				
<b>BLAs only:</b> Companion application received if a shared or divided manufacturing arrangement?  <b>If yes, BLA #</b>			<b>X</b>	
<b>Forms and Certifications</b>				
<i>Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, <b>paper</b> forms and certifications with hand-written signatures must be included. <b>Forms</b> include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); <b>Certifications</b> include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i>				
<b>Application Form</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)?  <i>If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].</i>	X			
Are all establishments and their registration numbers listed on the form/attached to the form?	X			
<b>Patent Information (NDAs/NDA efficacy supplements only)</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	X			
<b>Financial Disclosure</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)?  <i>Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].</i>  <i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i>	X			
<b>Clinical Trials Database</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is form FDA 3674 included with authorized signature?  <i>If yes, ensure that the application is also coded with the supporting document category, "Form 3674."</i>  <i>If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant</i>	X			
<b>Debarment Certification</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>

<p>Is a correctly worded Debarment Certification included with authorized signature?</p> <p><i>Certification is not required for supplements if submitted in the original application; If foreign applicant, both the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].</i></p> <p><i>Note: Debarment Certification should use wording in FDCA Section 306(k)(1) i.e., “[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.” Applicant may not use wording such as, “To the best of my knowledge...”</i></p>	X			Signed by Andrew Cheng, SVP, HIV Therapeutics & Development Operations
<b>Field Copy Certification (NDAs/NDA efficacy supplements only)</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<p><b>For paper submissions only:</b> Is a Field Copy Certification (that it is a true copy of the CMC technical section) included?</p> <p><i>Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)</i></p> <p><i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i></p>			X	This is an electronic submission
<b>Controlled Substance/Product with Abuse Potential</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<p><u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)?</p> <p><i>If yes, date consult sent to the Controlled Substance Staff:</i></p> <p><u>For non-NMEs:</u> <i>Date of consult sent to Controlled Substance Staff:</i></p>			X	
<b>Pediatrics</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<p><b><u>PREA</u></b></p> <p>Does the application trigger PREA?</p> <p><i>If yes, notify PeRC RPM (PeRC meeting is required)<sup>2</sup></i></p> <p><i>Note: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver &amp; deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i></p>	X			PeRC meeting has been scheduled

<sup>2</sup> <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027829.htm>

<b>If the application triggers PREA</b> , are the required pediatric assessment studies or a full waiver of pediatric studies included?		X		(b) (4) waiver request for pediatric population under 6 years of age
<b>If studies or full waiver not included</b> , is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included?  <i>If no, request in 74-day letter</i>	X			
<b>If a request for full waiver/partial waiver/deferral is included</b> , does the application contain the certification(s) required by FDCA Section 505B(a)(3) and (4)?  <i>If no, request in 74-day letter</i>	X			Request deferral for subjects 6 to < 18 years of age.
<b>BPCA (NDAs/NDA efficacy supplements only):</b>  Is this submission a complete response to a pediatric Written Request?  <i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)<sup>3</sup></i>		X		This is the original application
<b>Proprietary Name</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is a proposed proprietary name submitted?  <i>If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."</i>	X			Sponsor submitted new proprietary name request on December 13, 2011 (Proposed name (b) (4))
<b>REMS</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is a REMS submitted?  <i>If yes, send consult to OSE/DRISK and notify OC/OSI/DSC/PMSB via the DCRMSRMP mailbox</i>		X		
<b>Prescription Labeling</b>	<input type="checkbox"/> <b>Not applicable</b>			
Check all types of labeling submitted.	<input checked="" type="checkbox"/> Package Insert (PI) <input checked="" type="checkbox"/> Patient Package Insert (PPI) <input type="checkbox"/> Instructions for Use (IFU) <input type="checkbox"/> Medication Guide (MedGuide) <input checked="" type="checkbox"/> Carton labels <input checked="" type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent <input type="checkbox"/> Other (specify)			
	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is Electronic Content of Labeling (COL) submitted in SPL format?  <i>If no, request applicant to submit SPL before the filing date.</i>	X			
Is the PI submitted in PLR format? <sup>4</sup>	X			

<sup>3</sup> <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027837.htm>

<b>If PI not submitted in PLR format</b> , was a waiver or deferral requested before the application was received or in the submission? <b>If requested before application was submitted</b> , what is the status of the request?  <i>If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.</i>			X	
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to DDMAC?	X			
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (send WORD version if available)	X			PPI consult sent to PLT- Sharon Mills is the reviewer. PI, and carton/container label sent to OSE/DMEPA, Morgan Walker-reviewer, Consult sent to DDMAC for PI, PPI and carton/container.
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	X			Doug Campbell-OMPQ reviewer
<b>OTC Labeling</b>	<input checked="" type="checkbox"/> <b>Not Applicable</b>			
Check all types of labeling submitted.	<input type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify)			
	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is electronic content of labeling (COL) submitted?  <i>If no, request in 74-day letter.</i>				
Are annotated specifications submitted for all stock keeping units (SKUs)?  <i>If no, request in 74-day letter.</i>				
If representative labeling is submitted, are all represented SKUs defined?  <i>If no, request in 74-day letter.</i>				
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?				
<b>Other Consults</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>

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<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm>

Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team)		X		
<i>If yes, specify consult(s) and date(s) sent:</i>				
<b>Meeting Minutes/SPAs</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
End-of Phase 2 meeting(s)? <b>Date(s):</b> March 12, 2010 (IND (b)(4))  January 14, 2009 meeting to discuss integrated development and registration plans for elvitegravir, cobicistat and EVG/COBI/FTAC/TDF fixed-dose combination tablets  <i>If yes, distribute minutes before filing meeting</i>	X			Preliminary comments sent January 13, 2009
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? <b>Date(s):</b> July 13, 2011  <i>If yes, distribute minutes before filing meeting</i>		X		The July 13, 2011 pre-NDA meeting was cancelled by the sponsor after receiving our July 8, 2011, preliminary comments
Any Special Protocol Assessments (SPAs)? <b>Date(s):</b> IND (b)(4): April 19, 2009 submitted mouse and rat  <i>If yes, distribute letter and/or relevant minutes before filing meeting</i>	X			Response from Executive CAC on May 27, 2009

ATTACHMENT

**MEMO OF FILING MEETING**

**DATE:** December 16, 2011

**BLA/NDA/Supp #:** 203-100

**PROPRIETARY NAME:** Undetermined

**ESTABLISHED/PROPER NAME:** Elvitegravir/Cobicistat/Emtricitabine/Tenofovir Disoproxil Fumarate (EVG/COBI/FTC/TDF) 150/150/200/300 mg Single Tablet Regimen (STR)

**DOSAGE FORM/STRENGTH:** 150/150/200/300 mg Single Tablet Regimen

**APPLICANT:** Gilead Sciences, Inc.

**PROPOSED INDICATION(S)/PROPOSED CHANGE(S):** Treatment of HIV-1 Infection.

**BACKGROUND:** The original application for NDA 203-100, Single Tablet Regimen of EVG/COBI/FTC/TDF 150/150/200/300 mg was submitted on October 26, 2011 for the treatment of HIV-1 infection in adults. Emtricitabine and tenofovir disoproxil fumarate are approved NRTIs for the treatment of HIV-1 as stand-alone agents or in fixed-dose combination products: Emtriva (emtricitabine), Viread (tenofovir DF), Truvada (emtricitabine/tenofovir), Atripla (efavirenz, emtricitabine/tenofovir DF), and Complera (emtricitabine/rilpivirine/tenofovir DF). Elvitegravir is an integrase strand transfer inhibitor studied under IND (b) (4) and cobicistat is a cytochrome P4503A inhibitor studied under IND (b) (4).

**REVIEW TEAM:**

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Stacey Min	Y
	CPMS/TL:	Victoria Tyson	Y
Cross-Discipline Team Leader (CDTL)	Linda Lewis		Y
Clinical	Reviewer:	Adam Sherwat	Y
	TL:	Linda Lewis	Y
Social Scientist Review (for OTC products)	Reviewer:	n/a	
	TL:	n/a	
OTC Labeling Review (for OTC	Reviewer:	n/a	

<i>products)</i>			
	TL:	n/a	
Clinical Microbiology ( <i>for antimicrobial products)</i>	Reviewer:	Sung Rhee Takashi Komatsu	
	TL:	Julian O’Rear	

Clinical Pharmacology	Reviewer:	Vikram Arya	Y
	TL:	Kellie Reynolds	Y
Biostatistics	Reviewer:	Wen Zeng	Y
	TL:	Daphne Lin Guoxing Soon Fraser Smith	Y N Y
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Pritam Verma Peyton Myers	N Y
	TL:	Hanan Ghantous	Y
Statistics (carcinogenicity)	Reviewer:		
	TL:		
Immunogenicity (assay/assay validation) ( <i>for BLAs/BLA efficacy supplements</i> )	Reviewer:		
	TL:		
Product Quality (CMC)	Reviewer:	Celia Cruz Milton Sloan Fuqiang Liu	Y N Y
	TL:	Rapti Madurawe Stephen Miller	N Y
Quality Microbiology ( <i>for sterile products</i> )	Reviewer:		
	TL:		
CMC Labeling Review	Reviewer:		
	TL:		
Facility Review/Inspection	Reviewer:	Deepika Lakhani	N
	TL:		
OSE/DMEPA (proprietary name)	Reviewer:	Morgan Walker	Y
	TL:	Irene Chan	N

OSE/DRISK (REMS)	Reviewer:	Sharon Mills	Y
	TL:	Barbara Fuller	N
OC/OSI/DSC/PMSB (REMS)	Reviewer:		
	TL:		

Bioresearch Monitoring (DSI)	Reviewer:	Antoine El Hage	N
	TL:		
Controlled Substance Staff (CSS)	Reviewer:		
	TL:		
Other reviewers	Pravin Jadhav, Pharmacometrics TL		Y
Other attendees	Paul Tran, AC		Y

**FILING MEETING DISCUSSION:**

<b>GENERAL</b>	
<ul style="list-style-type: none"> <li>505(b)(2) filing issues?</li> </ul> <p><b>If yes, list issues:</b></p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> <li>Per reviewers, are all parts in English or English translation?</li> </ul> <p><b>If no, explain:</b></p>	<input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> <li>Electronic Submission comments</li> </ul> <p><b>List comments:</b></p>	<input type="checkbox"/> Not Applicable
<b>CLINICAL</b>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input checked="" type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> <li>Clinical study site(s) inspections(s) needed?</li> </ul> <p><b>If no, explain:</b></p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> <li>Advisory Committee Meeting needed?</li> </ul>	<input checked="" type="checkbox"/> YES

<p><b>Comments:</b></p> <p><i>If no, for an original NME or BLA application, include the reason. For example:</i></p> <ul style="list-style-type: none"> <li>○ <i>this drug/biologic is not the first in its class</i></li> <li>○ <i>the clinical study design was acceptable</i></li> <li>○ <i>the application did not raise significant safety or efficacy issues</i></li> <li>○ <i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i></li> </ul>	<p>Date if known: May 17, 2012</p> <p><input type="checkbox"/> NO</p> <p><input type="checkbox"/> To be determined</p> <p>Reason: NME</p>
<ul style="list-style-type: none"> <li>• Abuse Liability/Potential</li> </ul> <p><b>Comments:</b></p>	<p><input checked="" type="checkbox"/> Not Applicable</p> <p><input type="checkbox"/> FILE</p> <p><input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>
<ul style="list-style-type: none"> <li>• If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance?</li> </ul> <p><b>Comments:</b></p>	<p><input checked="" type="checkbox"/> Not Applicable</p> <p><input type="checkbox"/> YES</p> <p><input type="checkbox"/> NO</p>
<p><b>CLINICAL MICROBIOLOGY</b></p> <p><b>Comments:</b></p>	<p><input type="checkbox"/> Not Applicable</p> <p><input checked="" type="checkbox"/> FILE</p> <p><input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>
<p><b>CLINICAL PHARMACOLOGY</b></p> <p><b>Comments:</b></p>	<p><input type="checkbox"/> Not Applicable</p> <p><input checked="" type="checkbox"/> FILE</p> <p><input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>
<ul style="list-style-type: none"> <li>• Clinical pharmacology study site(s) inspections(s) needed?</li> </ul>	<p><input checked="" type="checkbox"/> YES</p> <p><input type="checkbox"/> NO</p>
<p><b>BIOSTATISTICS</b></p> <p><b>Comments:</b></p>	<p><input checked="" type="checkbox"/> Not Applicable</p> <p><input type="checkbox"/> FILE</p> <p><input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>
<p><b>NONCLINICAL</b></p>	<p><input type="checkbox"/> Not Applicable</p>

<p><b>(PHARMACOLOGY/TOXICOLOGY)</b></p> <p>Comments:</p>	<input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p><b>IMMUNOGENICITY (BLAs/BLA efficacy supplements only)</b></p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p><b>PRODUCT QUALITY (CMC)</b></p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p><b><u>Environmental Assessment</u></b></p> <ul style="list-style-type: none"> <li>• Categorical exclusion for environmental assessment (EA) requested?</li> </ul> <p style="padding-left: 40px;">If no, was a complete EA submitted?</p> <p style="padding-left: 40px;">If EA submitted, consulted to EA officer (OPS)?</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
<p><b><u>Quality Microbiology (for sterile products)</u></b></p> <ul style="list-style-type: none"> <li>• Was the Microbiology Team consulted for validation of sterilization? (NDAs/NDA supplements only)</li> </ul> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<p><b><u>Facility Inspection</u></b></p> <ul style="list-style-type: none"> <li>• Establishment(s) ready for inspection?</li> <li>▪ Establishment Evaluation Request (EER/TBP-EER) submitted to DMPQ?</li> </ul> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO

<p><b><u>Facility/Microbiology Review (BLAs only)</u></b></p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p><b><u>CMC Labeling Review</u></b></p> <p>Comments:</p>	<input type="checkbox"/> Review issues for 74-day letter
<b>REGULATORY PROJECT MANAGEMENT</b>	
<p><b>Signatory Authority:</b> Edward Cox, M.D., MPH</p> <p><b>21<sup>st</sup> Century Review Milestones (see attached)</b> (listing review milestones in this document is optional):</p> <p>Comments:</p>	
<b>REGULATORY CONCLUSIONS/DEFICIENCIES</b>	
<input type="checkbox"/>	The application is unsuitable for filing. Explain why:
<input checked="" type="checkbox"/>	The application, on its face, appears to be suitable for filing. <u>Review Issues:</u> <input type="checkbox"/> No review issues have been identified for the 74-day letter. <input checked="" type="checkbox"/> Review issues have been identified for the 74-day letter. List (optional): <u>Review Classification:</u> <input checked="" type="checkbox"/> Standard Review <input type="checkbox"/> Priority Review
<b>ACTIONS ITEMS</b>	
<input type="checkbox"/>	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug).
<input type="checkbox"/>	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
<input type="checkbox"/>	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.

<input type="checkbox"/>	BLA/BLA supplements: If filed, send 60-day filing letter
<input type="checkbox"/>	If priority review: <ul style="list-style-type: none"> <li>• notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices)</li> <li>• notify DMPQ (so facility inspections can be scheduled earlier)</li> </ul>
<input type="checkbox"/>	Send review issues/no review issues by day 74
<input type="checkbox"/>	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
<input type="checkbox"/>	BLA/BLA supplements: Send the Product Information Sheet to the product reviewer and the Facility Information Sheet to the facility reviewer for completion. Ensure that the completed forms are forwarded to the CDER RMS-BLA Superuser for data entry into RMS-BLA one month prior to taking an action [These sheets may be found at: <a href="http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027822">http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027822</a> ]
<input type="checkbox"/>	Other

Stacey Min

Regulatory Project Manager

Date

Victoria Tyson

Chief, Project Management Staff

Date

## Appendix A (NDA and NDA Supplements only)

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original application is likely to be a 505(b)(2) application if:

- (1) it relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application,
- (2) it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval, or
- (3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies),
- (2) No additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application, and.
- (3) All other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely

for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),
- (2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or
- (3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your OND ADRA or OND IO.

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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STACEY MIN  
01/17/2012

VICTORIA L TYSON  
01/17/2012