CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

212887Orig1s000
212888Orig1s000

PRODUCT QUALITY REVIEW(S)

U.S. FOOD & DRUG ADMINISTRATION

RECOMMENDATION

☒ Approval
☐ Approval with Post-Marketing Commitment
☐ Complete Response

NDA 212887
Assessment # 2

Drug Product Name	Vocabria, cabotegravir tablets
Dosage Form	Tablets
Strength	30 mg
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	Viiv Healthcare
US agent, if applicable	NA

Submission(s) Assessed	Document Date	Discipline(s) Affected
eCTD 0041	07/28/2020	NDA resubmission
eCTD 0042	11/30/2020	Labeling

QUALITY ASSESSMENT TEAM

Discipline	Primary Assessment	Secondary Assessment
Drug Substance	Kabir M Shahjahan	Haripada Sarkar
Drug Product	Peter Guerrieri	Erika Englund
Manufacturing	Chungsheng Cai	Bo Jiang
Microbiology	NA	
Biopharmaceutics	NA	
Regulatory Business Process Manager	Shamika Brooks and Anh-Thy Ly	
Application Technical Lead	Erika Englund	
Laboratory (OTR)	NA	
Environmental	NA	

QUALITY ASSESSMENT DATA SHEET

IQA NDA Assessment Guide Reference

1. **RELATED/SUPPORTING DOCUMENTS:** Refer to CMC review #1

EXECUTIVE SUMMARY

IQA NDA Assessment Guide Reference

I. RECOMMENDATIONS AND CONCLUSION ON APPROVABILITY

The NDA, as amended, has provided adequate CMC information to assure the identity, strength, purity, and quality of the proposed drug product. Therefore, this NDA is recommended for approval by the Office of Pharmaceutical Quality (OPQ) at this time. The manufacturing and testing facilities for this NDA are deemed acceptable and an overall "Approve" recommendation was entered into Panorama on 9/1/2020.

II. SUMMARY OF QUALITY ASSESSMENTS

A. Product Overview

The proposed product (cabotegravir tablets) is a HIV-1 integrase strand transfer inhibitor (INSTI) and is indicated in combination with Edurant (rilpivirine) for short-term use in adults with HIV-1 infection. The tablets will be an oral lead-in (OLI) to assess the tolerability of cabotegravir prior to administration of the extended release injectable suspension of Cabenuva (cabotegravir, rilpivirine) injectable suspension. Refer to NDA 212888 for the discussion of the extended release injectable suspension. The tablets will also provide oral therapy for patients who will miss planned dosing of the extended release injectable suspensions in Cabenuva.

The tablets are white, film-coated, oval tablets debossed with "SV CTV" on one side. Each film-coated tablet contains 30 mg of cabotegravir (equivalent to 31.62 mg cabotegravir sodium). The recommended dose is one 30 mg tablet taken once daily for approximately 1 month.

This NDA was recommended for approval in CMC Review #1 dated 11/07/2019; however, NDA 212888 was recommended for a CR due to CMC deficiencies. Since the approval of NDA 212887 was contingent on the approval of NDA 212888, NDA 212887 received a Complete Response Letter on 12/19/2020. A complete response was submitted on 07/28/2020, and this NDA is recommended for approval from a CMC perspective.

Proposed Indication(s) including Intended Patient Population	Indicated, in combination with Edurant (rilpivirine), for short-term use in adults with HIV-1 infection
Duration of Treatment	Once daily for approximately 1 month
Maximum Daily Dose	30 mg
Alternative Methods of Administration	Refer to NDA 212888 regarding the cabotegravir extended release injection. There are no alternative methods of administration for the tablets.

B. Quality Assessment Overview

Drug Substance: Adequate

The NDA was recommended for approval from a drug substance perspective in review #1. In the NDA resubmission, the drug substance CMC information in the NDA was unchanged, therefore, this NDA is still recommended for approval from a drug substance perspective.

For additional details, refer to the review by Kabir Shahjahan, Ph.D.

Drug Product: Adequate

N/A. This NDA was recommended for approval in CMC Review #1 from a drug product perspective.

Labeling: Adequate

The labeling was found adequate in CMC Review #1. The applicant submitted a revised container label with the NDA resubmission, and the revisions are acceptable from a drug product perspective.

For additional details, refer to the labeling review by Peter Guerrieri, Ph.D.

Manufacturing: Adequate

N/A. This NDA was recommended for approval from a manufacturing perspective in CMC Review #1

The Overall Manufacturing Inspection recommendation was entered as "Approve" on 9/1/2020.

Biopharmaceutics: Adequate

N/A. This NDA was recommended for approval in CMC Review #1 from a biopharmaceutics perspective.

Microbiology (if applicable): Choose an item.

NA

C. Risk Assessment- Refer to Review #1

D. List of Deficiencies for Complete Response

1. Overall Quality Deficiencies (Deficiencies that affect multiple sub-disciplines)

None

2. Drug Substance Deficiencies

3. Drug Product Deficiencies

4. Labeling Deficiencies

5. Manufacturing Deficiencies

6. Biopharmaceutics Deficiencies

7. Microbiology Deficiencies

8. Other Deficiencies (Specify discipline, such as Environmental)

Application Technical Lead Name and Date:

Erika Englund

Digitally signed by Erika Englund
Date: 12/18/2020 09:30:28AM
GUID: 51389ea30003450414230afb8c3e8114

CHAPTER I: DRUG SUBSTANCE

Drug Substance Name	Cabotegravir sodium
NDA Number	212887
Assessment Cycle Number	02
DMF Number (If Applicable)	NA
DMF Status	**Adequate**
Applicant Name	ViiV Healthcare Company
DMF Holder	(b) (4)

Assessment Recommendation: **Adequate**

DS Review Summary

Background:

The applicant, ViiV Healthcare, submitted original NDA 212887 for FDA's regulatory review and action on April 29, 2019, for drug product cabotegravir oral tablets (VOCABRIA) to the Division of Antivirals (DAV), FDA. The Agency informed the applicant, ViiV Healthcare, that the NDAs could not be approved in their present forms via Complete Response Letters (CRLs), dated December 19, 2020, The CRLs were communicated to the applicant on December 20, 2019. Later, the applicant, ViiV Healthcare, resubmitted the NDA 212887 application to the DAV, FDA, dated 07.28.2020 for regulatory review and action in response to the CRLs.

Drug Substance Evaluation*:*
The drug substance (DS) review for the original NDA 212887, submitted on April 29, 2019, was found to be adequate by the same reviewer, Dr. Kabir Shahjahan, dated 10.31.2019. The drug substance CMC information remains unchanged compared to the resubmission of this NDA 212887 (SD # 41), dated 07/28/2020. Therefore, the evaluation of the DS CMC information is not required for this NDA

212887 resubmission. Please refer to the drug substance review, Review #01, dated 10.31.2019 for NDA 212887 for detailed DS review.

List Submissions being assessed (Table) in the NDA 212887 Submission:

Document(s) Assessed	Date Received
Proprietary Name/Request for Review; NDA Resubmission/Class 2; Form 3674	SD# 41; eCTD# 0041: 07/28/2020

3.2.R Regional Information

Reviewer's Assessment: ***{Adequate/Inadequate}***

NA

Comparability Protocols

Reviewer's Assessment: ***{Adequate/Inadequate}***

NA

Post-Approval Commitments (For NDA only)

Reviewer's Assessment: ***{Adequate/Inadequate}***

NA

Lifecycle Management Considerations

NA

List of Deficiencies:

None

List of Deficiencies:

None

Primary Drug Substance Reviewer Name and Date:

Kabir M Shahjahan, PhD
FDA/CDER/OPQ/ONDP/DND/API/Branch 1
09-November-2020

Secondary Reviewer Name and Date:
Haripada Sarkar, Ph.D.; QAL
FDA/CDER/OPQ/ONDP/DND/API/Branch 1
09-November-2020

Kabir Shahjahan

Digitally signed by Kabir Shahjahan
Date: 11/09/2020 09:34:44AM
GUID: 598df2610046f5d0e3dc5da287df54aa

Haripada Sarker

Digitally signed by Haripada Sarker
Date: 11/12/2020 12:32:24PM
GUID: 507d82ab00005f362bcd357373643206

DRUG PRODUCT LABELING MEMORANDUM TO FILE	
DMF Number	212887 (SN-0042)
Type of Submission	Labeling/Container-Carton Draft
Drug Product/Route of administration	VOCABRIA (cabotegravir) tablets, 30 mg for oral administration
Applicant/Sponsor	ViiV Healthcare Company (ViiV)
Date of Memo	12/07/2020
Drug Product Primary/Secondary Reviewers	Pete Guerrieri, Ph.D. (primary) Erika Englund, Ph.D. (secondary)

EXECUTIVE SUMMARY:

The applicant submitted a revised container label on 11/30/2020, in response to DMEPA recommendations. The revisions are acceptable from a drug product perspective.

REVIEW:

On 11/20/2020, DMEPA recommended to the applicant that an alert box be included on the VOCABRIA display panel on the container label (30 mg) to alert end uses about medications that should not be taken with VOCABRIA. A revised container label was submitted on 11/30/2020 which included the recommended alert box. DMEPA reviewed the container label and deemed it acceptable (Memo in DARRTS filed 12/01/2020). No other changes to information in the label were made, which was deemed adequate from a CMC perspective in the original review cycle (11/18/2019). The label is adequate from drug product perspective, and no further comments are recommended.

1 Page of Draft Labeling has been Withheld in Full as b4 (CCI/TS) immediately following this page

Peter Guerrieri

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Date: 12/10/2020 01:06:51PM
GUID: 54eb8ba100062ea99cbaab7c64143df3

Erika Englund

Digitally signed by Erika Englund
Date: 12/14/2020 07:08:15PM
GUID: 51389ea30003450414230afb8c3e8114

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/s/

ERIKA E ENGLUND
12/18/2020 09:59:55 AM

U.S. FOOD & DRUG ADMINISTRATION

RECOMMENDATION

☒ Approval
☐ Approval with Post-Marketing Commitment
☐ Complete Response

NDA # 212887
Assessment # 2

Drug Product Name	Vocabria, cabotegravir tablets
Dosage Form	Tablets
Strength	30 mg
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	Viiv Healthcare
US agent, if applicable	NA

Submission(s) Assessed	Document Date	Discipline(s) Affected
eCTD 0033	11/12/2019	DP

QUALITY ASSESSMENT TEAM, RELATED/SUPPORTING DOCUMENTS, DMFs, and Consults: Refer to Review #1

EXECUTIVE SUMMARY

I. RECOMMENDATIONS AND CONCLUSION ON APPROVABILITY

The NDA, as amended, has provided adequate CMC information to assure the identity, strength, purity, and quality of the proposed drug product. Therefore, this NDA is recommended for approval by the Office of Pharmaceutical Quality (OPQ) at this time. The manufacturing and testing facilities for this NDA are deemed acceptable and an overall "Approve" recommendation was entered into Panorama by the Office of Process and Facilities (OPF) on August 22, 2019.

II. SUMMARY OF QUALITY ASSESSMENTS

A. Product Overview

Refer to Review #1

B. Quality Assessment Overview

Drug Substance: Adequate

Refer to Review #1

Drug Product: Adequate

At the time of Review #1, the regulatory specifications did not include a test for (b) (4). The lack of (b) (4) testing was not considered an approvability issue, but due to the limited manufacturing experience, the team considered this an important test that should be included. The following IR was sent on 11/6/2019:

There is insufficient manufacturing experience and batch history at this time to justify the absence of a (b) (4) specification in the drug product release/regulatory (stability) specifications. Please amend the drug product specification to include a specification limit for (b) (4) testing at release and on stability, based on primary stability batch results and other relevant batch history.

The applicant included the recommended testing in the 11/12/2019 amendment, and this update was found acceptable in the drug product review.

For additional details, refer to the addendum to the drug product review by Peter Guerrieri.

Labeling: Adequate

Labeling recommendations were communicated to the OND PM

Manufacturing: Adequate

Refer to Review #1

Biopharmaceutics: Adequate

Refer to Review #1

Microbiology (if applicable): Choose an item.

NA

C. Risk Assessment

Refer to Review #1

D. List of Deficiencies for Complete Response

1. Overall Quality Deficiencies (Deficiencies that affect multiple sub-disciplines)

None

2. Drug Substance Deficiencies

3. Drug Product Deficiencies

4. Labeling Deficiencies

5. Manufacturing Deficiencies

6. Biopharmaceutics Deficiencies

7. Microbiology Deficiencies

8. Other Deficiencies (Specify discipline, such as Environmental)

Application Technical Lead Name and Date:

Erika E. Englund, Ph.D.

Erika Englund

Digitally signed by Erika Englund
Date: 12/11/2019 06:32:06PM
GUID: 51389ea30003450414230afb8c3e8114

NDA 212887 – Cabotegravir Tablets

Memo – Addendum with addition of [redacted] limit to drug product regulatory specifications

Date: 11/19/2019

Summary

The applicant had in their submission included [redacted] testing, but not a [redacted] test in the drug product specification. The review team determined that although risk was overall low for impact of [redacted] on critical drug product attributes, there was insufficient batch or manufacturing history to support the absence of a [redacted] test with limit. This was communicated to the applicant via IR on 11/07/19, and the applicant responded in the amendment dated 11/12/2019. In their response, the applicant added a [redacted] test to the drug product specification with a limit of NMT [redacted]%, based on statistical analysis of stability batches and considering in-use stability results. The limit is appropriate based on evaluation of their stability results, with no impact on critical drug product attributes for [redacted] throughout the range [redacted]%. The applicant's response is adequate.

Peter Guerrieri

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Date: 11/19/2019 12:11:02PM
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Erika Englund

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Date: 11/19/2019 04:07:08PM
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CHAPTER IV: LABELING

IQA NDA Assessment Guide Reference

1.0 PRESCRIBING INFORMATION

Assessment of Product Quality Related Aspects of the Prescribing Information:

1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION

Item	Information Provided in the NDA	Assessor's Comments
Product Title in Highlights		
Proprietary name	VOCABRIA (cabotegravir) tablets, for oral use	Adequate.
Established name(s)	Cabotegravir tablets	Adequate.
Route(s) of administration	Oral	Adequate.
Dosage Forms and Strengths Heading in Highlights		
Summary of the dosage form(s) and strength(s) in metric system.	Tablets: 30 mg	Adequate.
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	N/A	

1.2 FULL PRESCRIBING INFORMATION

1.2.1 Section 2 (DOSAGE AND ADMINISTRATION)

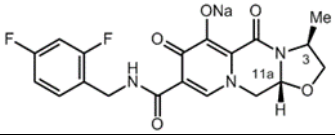
Item	Information Provided in the NDA	Assessor's Comments
DOSAGE AND ADMINISTRATION section		
Special instructions for product preparation (e.g., reconstitution and resulting concentration, dilution, compatible diluents, storage conditions needed to maintain the stability of the reconstituted or diluted product)	N/A	

1.2.2 Section 3 (DOSAGE FORMS AND STRENGTHS)

Item	Information Provided in the NDA	Assessor's Comments
DOSAGE FORMS AND STRENGTHS section		
Available dosage form(s)	VOCABRIA tablets are white, film-coated, oval tablets debossed with "SV CTV" on one side. Each film-coated tablet contains 30 mg of cabotegravir (equivalent to 31.62 mg cabotegravir sodium).	Adequate.
Strength(s) in metric system	30 mg	Adequate.
If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance	See above	Adequate. Adheres to salt policy.
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting	White, film-coated, oval tablets debossed with "SV CTV" on one side.	Adequate.
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	Not scored	
For injectable drug products for parental administration, use appropriate labeling term (e.g., single-dose, multiple-dose, single-patient-use). Other package type terms include pharmacy bulk package and imaging bulk package.	N/A	

1.2.3 Section 11 (DESCRIPTION)

Item	Information Provided in the NDA	Assessor's Comments
DESCRIPTION section		
Proprietary and established name(s)	VOCABRIA (Cabotegravir)	Adequate
Dosage form(s) and route(s) of administration	Immediate-release tablet for oral administration	Adequate
If the active ingredient is a salt, apply the USP Salt Policy and include the equivalency statement per FDA Guidance.	contains 30 mg of cabotegravir (equivalent to 31.62 mg cabotegravir sodium)	Adequate. The salt equivalency statement per the Salt Policy is included.
List names of all inactive ingredients. Use USP/NF names. Avoid Brand names.	inactive ingredients: hypromellose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, and sodium starch glycolate. The tablet film-coating contains hypromellose, polyethylene glycol, and titanium dioxide.	Adequate.
For parenteral injectable dosage forms, include the name and quantities of all inactive ingredients. For ingredients added to adjust the pH or make isotonic, include the name and statement of effect.	N/A	
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	N/A	
Statement of being sterile (if applicable)	N/A	
Pharmacological/ therapeutic class	HIV INSTI	Adequate.

Chemical name, structural formula, molecular weight	The chemical name of cabotegravir sodium is sodium (*3S,11aR*)-N-[(2,4-difluorophenyl)methyl]-6-hydroxy-3-methyl-5,7-dioxo-2,3,5,7,11,11a-hexahydro[1,3]oxazolo[3,2-a]pyrido [1,2-d]pyrazine-8-carboxamide. The empirical formula is $C_{19}H_{16}F_2N_3NaO_5$ and the molecular weight is 427.34 g/mol. It has the following structural formula: 	Adequate.
If radioactive, statement of important nuclear characteristics.	N/A	
Other important chemical or physical properties (such as pKa or pH)	Cabotegravir sodium is a white to almost white crystalline solid that is slightly soluble in water.	Adequate.

1.2.4 Section 16 (HOW SUPPLIED/STORAGE AND HANDLING)

Item	Information Provided in the NDA	Assessor's Comments
HOW SUPPLIED/STORAGE AND HANDLING section		
Available dosage form(s)	Each VOCABRIA tablet contains 30 mg of cabotegravir and is a white, oval, film-coated, biconvex (b) (4) tablet debossed with "SV CTV" on one side.	Adequate.
Strength(s) in metric system	30 mg	Adequate.
Available units (e.g., bottles of 100 tablets)	Bottle of 30 tablets with child-resistant closure NDC 49702-248-13.	Adequate.
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	See above	Adequate.
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	N/A	

Section 16 (HOW SUPPLIED/STORAGE AND HANDLING) (Continued)

Item	Information Provided in the NDA	Assessor's Comments

Special handling about the supplied product (e.g., protect from light, refrigerate). If there is a statement to “Dispense in original container,” provide reason why (e.g. to protect from light or moisture, to maintain stability, etc.)	N/A	
If the product contains a desiccant, ensure the size and shape differ from the dosage form and desiccant has a warning such as “Do not eat.”	N/A	
Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature.	Store below 30°C (86°F).	Adequate. This storage statement has been used with PEPFAR products. Although this submission is for U.S. approval, option this statement allows to harmonize with products that may be stored in Climatic Zone IVa/b, where stability studies have been conducted at 30°C/75% RH.
Latex: If product does not contain latex and manufacturing of product and container did not include use of natural rubber latex or synthetic derivatives of natural rubber latex, state: “Not made with natural rubber latex. Avoid statements such as “latex-free.”	N/A	
Include information about child-resistant packaging	Yes	Adequate.

1.2.5 Other Sections of Labeling

1.2.6 Manufacturing Information After Section 17 (for drug products)

Item	Information Provided in the NDA	Assessor's Comments
Manufacturing Information After Section 17		
Name and location of business (street address, city, state and zip code) of the manufacturer, distributor, and/or packer	GlaxoSmithKline Research Triangle Park, NC 27709	Adequate.

2.0 PATIENT LABELING

Assessment of Product Quality Related Aspects of Patient Labeling (e.g., Medication Guide, Patient Information, Instructions for Use):
The storage instructions in the Patient Information are appropriate, and instructions are included keep out of the reach of children.

3.0 CARTON AND CONTAINER LABELING

3.1 Container Label

See section 1.14

3.2 Carton Labeling

See section 1.14

Item	Information Provided in the NDA	Assessor's Comments about Carton Labeling
Proprietary name, established name, and dosage form (font size and prominence	VOCABRIA (cabotegravir) Tablets	Adequate.
Dosage strength	30 mg	Adequate.
Route of administration		
If the active ingredient is a salt, include the equivalency statement per FDA Guidance	Included (Each tablet contains 30 mg of cabotegravir equivalent to 31.62 mg of cabotegravir sodium.)	Adequate.
Net contents (e.g. tablet count)	30 tablets	Adequate.
"Rx only" displayed on the principal display	Yes	Adequate.
NDC number	49702-248-13	Adequate.
Lot number and expiration date	Yes	Adequate.
Storage conditions. If applicable, include a space on the carton labeling for the user to write the new BUD.	Store (b) (4) or below 30°C (86°F).	Adequate.
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use)	N/A	
Other package terms include pharmacy bulk package and imaging bulk package which require "Not for direct infusion" statement.	N/A	
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	N/A	
Bar code	Yes	Adequate.

Item	Information Provided in the NDA	Assessor's Comments about Carton Labeling
Name of manufacturer/distributor	GlaxoSmithKline RTP, NC 27709	Adequate.
Medication Guide (if applicable)	N/A	
No text on Ferrule and Cap overseal	Yes	Adequate.
When a drug product differs from the relevant USP standard of strength, quality, or purity, as determined by the application of the tests, procedures, and acceptance criteria set forth in the relevant compendium, its difference shall be plainly stated on its label.	N/A	
And others, if space is available	N/A	

Assessment of Carton and Container Labeling: *Adequate*

ITEMS FOR ADDITIONAL ASSESSMENT

N/A

Overall Assessment and Recommendation:

Based on this labeling review, the sections herein are adequate for approval.

Primary Labeling Assessor Name and Date:

Pete Guerrieri, PhD, Branch 3; Division of New Drug Product I.

Secondary Assessor Name and Date (and Secondary Summary, as needed):

Peter Guerrieri

Digitally signed by Peter Guerrieri
Date: 11/10/2019 08:36:30AM
GUID: 54eb8ba100062ea99cbaab7c64143df3

Balajee Shanmugam

Digitally signed by Balajee Shanmugam
Date: 11/12/2019 12:06:39PM
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/s/

ERIKA E ENGLUND
12/13/2019 09:17:29 AM

U.S. FOOD & DRUG ADMINISTRATION

RECOMMENDATION

☒ Approval
☐ Approval with Post-Marketing Commitment
☐ Complete Response

NDA # 212887

Assessment # 1

Drug Product Name	Vocabria, cabotegravir tablets
Dosage Form	Tablets
Strength	30 mg
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	Viiv Healthcare
US agent, if applicable	NA

Submission(s) Assessed	Document Date	Discipline(s) Affected
eCTD 0001	4/29/2019	All
eCTD 0003	5/3/2019	Proprietary Name
eCTD 0013	7/17/2019	Quality
eCTD 0016	8/5/2019	Quality
eCTD 0022	8/30/2019	Quality
eCTD 0023	9/16/2019	Quality
eCTD 0028	10/01/2019	Quality

QUALITY ASSESSMENT TEAM

Discipline	Primary Assessment	Secondary Assessment
Drug Substance	Kabir M Shahjahan	Haripada Sarkar
Drug Product	Peter Guerrieri	Thomas Oliver
Manufacturing	Chungsheng Cai	Bo Jiang
Microbiology	Chungsheng Cai	Bo Jiang
Biopharmaceutics	Akm Khairuzzaman	Elsbeth Chikhale
Regulatory Business Process Manager	Shamika Brooks	
Application Technical Lead	Erika Englund	
Laboratory (OTR)	NA	
Environmental	Raanan Bloom	Scott Furness

QUALITY ASSESSMENT DATA SHEET

IQA NDA Assessment Guide Reference

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Assessment Completed	Comments
NA	II	No Type II DMF was referenced, the drug substance information was submitted to the NDA				
Multiple	IV	Refer to the DP review regarding the container closure system				

B. OTHER DOCUMENTS: *IND, RLD, RS, Approved NDA*

Document	Application Number	Description
IND	101429	GSK1265744 Tablet
IND	109678	Cabotegravir and rilpivirine intramuscular injection
NDA	212888	Cabotegravir extended release Injectable suspension

2. CONSULTS

Discipline	Status	Recommendation	Date	Assessor
Biostatistics	NA			
Pharmacology/Toxicology	NA			
CDRH-ODE	NA			
CDRH-OC	NA			
Clinical	NA			
Other	NA			

EXECUTIVE SUMMARY

IQA NDA Assessment Guide Reference

I. RECOMMENDATIONS AND CONCLUSION ON APPROVABILITY

The NDA, as amended, has provided adequate CMC information to assure the identity, strength, purity, and quality of the proposed drug product. Therefore, this NDA is recommended for approval by the Office of Pharmaceutical Quality (OPQ) at this time. The manufacturing and testing facilities for this NDA are deemed acceptable and an overall "Approve" recommendation was entered into Panorama by the Office of Process and Facilities (OPF) on August 22, 2019.

II. SUMMARY OF QUALITY ASSESSMENTS

A. Product Overview

The proposed product (cabotegravir tablets) is a HIV-1 integrase strand transfer inhibitor (INSTI) and is indicated in combination with Edurant (rilpivirine) for short-term use in adults with HIV-1 infection. The tablets will be an oral lead-in (OLI) to assess the tolerability of cabotegravir prior to administration of the extended release injectable suspension of Cabenuva (cabotegravir, rilpivirine) injectable suspension. Refer to NDA 212888 for the discussion of the extended release injectable suspension. The tablets also will provide oral therapy for patients who will miss planned injection dosing. This product has fast track status, and the NDA included a Priority Review request.

The tablets are white, film-coated, oval tablets debossed with "SV CTV" on one side. Each film-coated tablet contains 30 mg of cabotegravir (equivalent to 31.62 mg cabotegravir sodium). The recommended dose is one 30 mg tablet taken once daily for approximately 1 month.

Proposed Indication(s) including Intended Patient Population	Indicated, in combination with Edurant (rilpivirine), for short-term use in adults with HIV-1 infection
Duration of Treatment	Once daily for approximately 1 month
Maximum Daily Dose	30 mg
Alternative Methods of Administration	Refer to NDA 212888 regarding the cabotegravir extended release injection. There are no alternative methods of administration for the tablets.

B. Quality Assessment Overview

Drug Substance: Adequate

The drug substance, cabotegravir sodium, is a chiral, white to almost white solid which is slightly soluble in water. It is manufactured in a (b) (4)

qualification threshold. Adequate assessment for mutagenic impurities was also carried out, and there is no significant risk identified of mutagenic impurities per ICH M7. The re-test period of the drug substance is (b) (4) months when stored at (b) (4) °C and (b) (4)

This NDA was recommended for approval from a drug substance perspective. For additional details, refer to the review by Kabir Shahjahan

Drug Product: Adequate

The drug product, Cabotegravir Tablets 30 mg are white film-coated, oval-shaped immediate release tablets for oral administration. The product is packaged into opaque, white high density polyethylene (HDPE) bottles with a (b) (4) child-resistant closure. All excipients in the product are compendial, and no overages are included in the formulation The phase 3 formulation is identical to the proposed commercial formulation.

(b) (4)

There are no specified impurities in the drug product specification, and any individual impurity is controlled to no greater than (b) (4)%. In addition, no elemental impurities were identified as having the potential to be present in Cabotegravir Tablets at a level of greater than (b) (4)% of the corresponding PDE limit for oral administration. The shelf life of the drug product is 24 months when stored below 30 °C.

The regulatory specifications did not include a test for (b) (4). The lack of (b) (4) testing is not considered an approvability issue, but due to the limited manufacturing experience, the team considered this an

important test that should be included. The following IR was sent on 11/6/2019:

There is insufficient manufacturing experience and batch history at this time to justify the absence of a (b) (4) *specification in the drug product release/regulatory (stability) specifications. Please amend the drug product specification to include a specification limit for* (b) (4) *testing at release and on stability, based on primary stability batch results and other relevant batch history.*

This pending request does not impact the approvability of the submission, and any subsequent update will be incorporated as an addendum to this OPQ IQA (b) (4)

This NDA is recommended for approval from a drug product perspective. For additional details, refer to the review by Peter Guerrieri.

Environmental Assessment:

The applicant's claim of categorical exclusion (21 CFR 25.31(b)) and provided statement of no extraordinary circumstance are acceptable. This was communicated in the Environmental Assessment review by Raanan Bloom.

Labeling: Adequate

Labeling recommendations were communicated to the OND PM

Manufacturing: Adequate

(b) (4)

No PAI's were requested for this NDA. The manufacturing and testing facilities for this are deemed acceptable and an overall "Approve" recommendation was entered into Panorama by the Office of Process and Facilities (OPF) on August 22, 2019.

This NDA is recommended for approval from a facilities and manufacturing perspective. For additional details, refer to the review by Chunsheng Cai.

Biopharmaceutics: Adequate

The Biopharmaceutics review was focused on the evaluation of the adequacy of the overall information/data supporting; 1) the proposed dissolution method and acceptance criteria, and 2) the bridging of multiple formulations throughout the drug product development.

Although no formal BCS designation was claimed, it appears the drug belongs to BCS class II based on solubility (insoluble pKa 1-7.8) and high permeability. The dissolution test method and acceptance criteria were found acceptable. The phase 3 tablet's formulation composition, image, and manufacturing site are identical to that of the proposed commercial product. Therefore, no further bridging is required.

This NDA is recommended for approval from a biopharmaceutics perspective. For additional details, refer to the review by Akm Khairuzzaman.

Microbiology (if applicable): Choose an item.

NA

C. Risk Assessment

From Initial Risk Identification			Assessment		
Attribute/ CQA	**Factors that can impact the CQA**	**Initial Risk Ranking**	**Risk Mitigation Approach**	**Final Risk Evaluation**	**Lifecycle Considerations / Comments**
Assay	Formulation, manufacture	Low	(b) (4)	Acceptable	
Physical stability	Formulation, manufacture	Medium		Acceptable	

			(b) (4)		
Content Uniformity	Formulation, manufacture	Low		Acceptable	
Microbial Limits	Formulation, manufacture raw materials	Low		Acceptable	
Dissolution	Formulation, manufacture raw materials. (b) (4)	Medium		Acceptable	The drug appears to be a BCS class II drug. Any change in (b) (4) and drug product manufacturing process may impact oral bioavailability. The Applicant should submit a prior approval supplement for any such changes during the lifecycle of the drug product.

D. List of Deficiencies for Complete Response

1. Overall Quality Deficiencies (Deficiencies that affect multiple sub-disciplines)

None

2. Drug Substance Deficiencies

3. Drug Product Deficiencies

4. Labeling Deficiencies

5. Manufacturing Deficiencies

6. Biopharmaceutics Deficiencies

7. Microbiology Deficiencies

8. Other Deficiencies (Specify discipline, such as Environmental)

Application Technical Lead Name and Date:

Erika E. Englund, Ph.D.

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U.S. FOOD & DRUG ADMINISTRATION

CHAPTER VI: BIOPHARMACEUTICS

Product Information	Vocabria Tablets
NDA Number	212887
Assessment Cycle Number	SDN 001
Drug Product Name/ Strength	Vocabria (cabotegravir sodium) Tablets, 30 mg
Route of Administration	Oral
Applicant Name	ViiV Healthcare Company
Therapeutic Classification/ OND Division	Antiviral Products
RLD/RS Number	N/A
Proposed Indication	Treatment of HIV

Assessment Recommendation: **Adequate**

Assessment Summary: The Biopharmaceutics review was focused on the evaluation of the adequacy of the overall information/data supporting; **1)** the proposed dissolution method and acceptance criteria, and **2)** the bridging of multiple formulations throughout the drug product development.

1. DISSOLUTION TEST:

Dissolution Method and Acceptance Criteria: The Applicant's proposed dissolution method [*USP apparatus II (Paddle) at 60±2 rpm; 1000±10 mL of 0.01M HCl with 0.2% CTAB at 37°C, UV, Filer used – 0.45 µ*] and acceptance criterion of Q= (b) (4)% at 25 min are ***acceptable*** for batch release and stability testing.

2. BRIDGING:

The Phase 3 tablet's formulation composition, image, and manufacturing site is identical to that of the commercial formulation. No further bridging is required. ***Acceptable***.

3. ***RISK ASSESSMENT:*** The table below shows the initial and final risk assessment for the CQA-dissolution.

CQAs	Initial Risk Ranking	Comments	Updated Risk Ranking after Assessment Cycle # SDN-013	Comments
Dissolution	Medium to high	(b) (4)	Low	An appropriate dissolution method has been developed and it's a part of the drug product specification. The proposed acceptance criterion is based on pivotal clinical batches dissolution data. Critical material attributes that may impact (b) (4)

List Submissions being assessed (table):

Document(s) Assessed	Date Received
SDN-001	04/29/2019
SDN-013	07/17/2019

Highlight Key Issues from Last Cycle and Their Resolution: None

Concise Description of Outstanding Issues (List bullet points with key information and update as needed): None

B.1 BCS DESIGNATION

Solubility data:

Table 1. Solubility data in various media

Solvent	Solubility (mg/mL)	Descriptor
Water	2.9 (at 25°C)	Slightly soluble
Acetonitrile	0.01 (at 20°C)	Practically insoluble
Dimethyl sulfoxide (DMSO)	3.81 (at 20°C)	Slightly soluble
Acetic acid	>102 (at 22°C)	Freely soluble

Solvent	Solubility at 37°C (mg/mL)	Descriptor
SGF pH 1.6	0.007	Practically insoluble
FaSSIF pH 6.5	0.019	Practically insoluble
FeSSIF pH 6.5	0.085	Practically insoluble

SGF Simulated Gastric Fluid
FeSSIF Fed State Simulated Intestinal Fluid
FaSSIF Fasted State Simulated Intestinal Fluid

Absorption: 76% oral bioavailability. T_{max} -3 hr.

Assessment: Acceptable
No formal BCS designation has been claimed. However, based on solubility and permeability data, it appears that the drug belongs to BCS class II.

Solubility: *Insoluble (pKa1-7.8, pKa2-1.1)*

Permeability: *High*

Dissolution: *Fast*

B.2 DISSOLUTION METHOD AND ACCEPTANCE CRITERIA

Dissolution Method Development:

The following table summarizes the different dissolution methods and their uses during the drug development

Table 2. Summary of dissolution methods evaluated during development

Method ID	*Method description*	*Limit Proposed*	*Clinical stage*	*Reviewer's Comments*
[redacted] (b) (4)				
D (proposed final method)	Apparatus 2 (Paddles) at 60 rpm in 1000 mL of 0.0125 M HCl, with 0.20% w/v cetyltrimethylammonium bromide (CTAB) maintained at 37°C	Q= (b) (4)% at 25 min	Phase 3	Has discriminating capability with respect to particle size distribution.

In accordance with ICH Q9, risk assessments using Failure Mode and Effects Analysis (FMEA) were used by the Applicant to determine which process parameters and attributes are likely to have the greatest impact on product quality. Critical API material attributes such as (b) (4) and particle size distribution were identified. Critical formulation and process risks were also identified. These risks were investigated (b) (4)

The effect of particle size distribution of cabotegravir sodium on human pharmacokinetics was evaluated in a clinical study (relative bioavailability study 2, study 201741). The data shows that drug product manufactured using (b) (4) drug substance resulted in an increase in both $AUC_{(0\text{-}inf)}$ and C_{max} when compared with drug product manufactured using (b) (4) drug substance. Based on the results the drug substance PSD is controlled to a specification of (b) (4)

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(b) (4)

The Applicant selected 0.20% CTAB. The **final proposed dissolution method** known as "**D**" is as follows:

Apparatus 2 (Paddles) at 60 rpm in 1000 mL of 0.0125 M HCl, with 0.20% w/v cetyltrimethylammonium bromide (CTAB) maintained at 37°C

Phase 3 clinical batches were tested for stability and dissolution data was generated using method "D". Data copied from the Application are presented below:

Table 3. Stability Data using dissolution method D for Cabotegravir Tablets, 30 mg (Phase 3 batch) stored in (b) (4)

Storage Condition	Time (MN)	Test									
		Description	Content (% Label Claim)	Drug-related Impurities (% area)			Dissolution (% Released)		(b) (4)		(b) (4)
				(b) (4)	Any individual impurity	Total Impurities[2]	Mean	Range			
Acceptance Criteria		See Note 1	(b) (4)	NGT (b)		NGT (b)	Q = (b) % at (b) (4) minutes				Report Result
Initial	0	Conforms	(b) (4)	(b) (4)		(b) (4)	95	(b) (4)			Conforms
5°C/AmbRH	12	Conforms					95				Conforms
	24	Conforms					95				Conforms
	36	Conforms					96				Conforms
25°C/60%RH	6	Conforms					98				Conforms
	12	Conforms					98				Conforms
	24	Conforms					94				Conforms
	36	Conforms					95				Conforms
30°C/75%RH packaged	3	Conforms					97				Conforms
	6	Conforms					97				Conforms
	9	Conforms					94				NT[4]
	12	Conforms					95				Conforms
	18	Conforms					94				Conforms
	24	Conforms					94				Conforms[5]
	36	Conforms					94				Conforms[5]
30°C/75%RH In-use	1	Conforms					95				Conforms
	3	Conforms					96				Conforms
	36	Conforms					95				Conforms[5]
40°C/75%RH	3	Conforms					95				Conforms
	6	Conforms					96				Conforms
50°C/AmbRH	1	Conforms					94				Conforms
	3	Conforms					96				Conforms

Table 4. Stability Data using dissolution method D for Cabotegravir Tablets, 30 mg (Phase 3 batch) stored in container closure system (b) (4)

Storage Condition	Time (MN)	Test								
		Description	Content (% Label Claim)	Drug-related Impurities (% area)			Dissolution (% Released)		(b) (4)	
				(b) (4)	Any individual impurity	Total Impurities[2]	Mean	Range		
Acceptance Criteria		See Note 1	(b) (4)				Q = (b) (4)% at (b) (4) minutes		Report Result	Report Result
Initial	0	Conforms					95	(b) (4)	(b) (4)	Conforms
5°C/AmbRH	12	Conforms					95			Conforms
	24	Conforms					95			Conforms
	36	Conforms					96			Conforms
25°C/60%RH	6	Conforms					98			Conforms
	12	Conforms					95			Conforms
	24	Conforms					94			Conforms
	36	Conforms					95			Conforms
30°C/75%RH packaged	3	Conforms					96			Conforms
	6	Conforms					97			Conforms
	9	Conforms					95			NT[4]
	12	Conforms					94			Conforms
	18	Conforms					95			Conforms
	24	Conforms					94			Conforms[5]
	36	Conforms					94			Conforms[5]
30°C/75%RH In-use	1	Conforms					94			Conforms
	3	Conforms					96			Conforms
	36	Conforms					95			Conforms[5]
40°C/75%RH	3	Conforms					95			Conforms
	6	Conforms					95			Conforms
50°C/AmbRH	1	Conforms					94			Conforms
	3	Conforms					96			Conforms

As exhibited in the above table, the dissolution acceptance criterion used was Q= (b) (4)% at (b) (4) min. Additionally, the applicant has mentioned that after long term storage for 24 and 36 months at 30°C/75% RH and for end of shelf life in-use stability (36 months) (b) (4) have been observed when the drug product is stored in container closure system (b) (4) The levels of (b) (4) are below the (b) (4)% reporting limit of the (b) (4) method. All stability batches, irrespective of low levels of (b) (4) met the dissolution specification in place at the time of testing (Q= (b) (4)% at (b) (4) minutes). However, the final proposed dissolution acceptance criterion is Q= (b) (4)% at 25 min.

The following dissolution profiles were submitted by the Applicant to show the final proposed dissolution method's discriminating capability with respect to API particle size distribution.

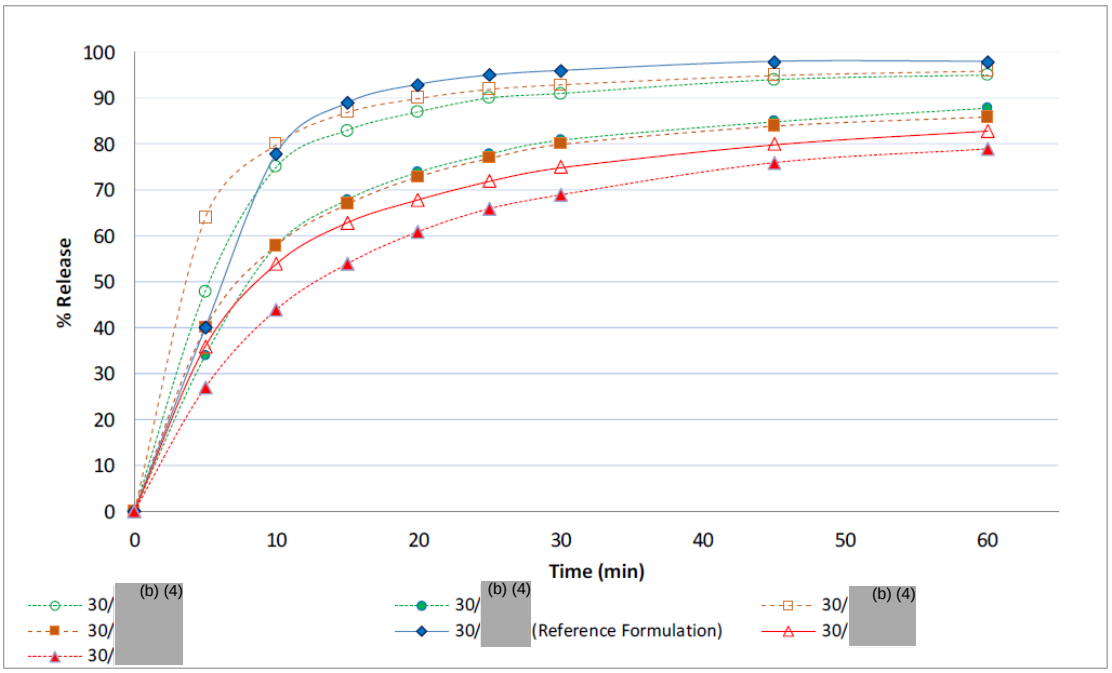

Fig 4. Dissolution of Formulations Evaluated in Relative Bioavailability Studies (LAI117020 and 201741) (Dissolution method D)

In the above figure 4, the batches designated with (b) (4) drug substance in the formulation. The number such as 30/(b) (4) represents the strength/finished tablet weight.

Assessment: ***Adequate***

Dissolution Method: *The following information was found missing in the initial submission:*

- *(i) There is no complete dissolution method development report in the submission.*
- *(ii) The dissolution acceptance criterion used for the Phase 3 clinical batches was Q= (b) (4)% in (b) (4) min., while the proposed specification is Q (b) (4)% in 25 min. It is not clear if the method used for the phase 3 clinical batches (Ref. Table 11 & 12, Section P.2.2) was the same as the proposed commercial dissolution method.*
- *(iii) It is not clear why 60 rpm was investigated and not (b) (4) rpm.*
- *(iv) Although the final method shows sensitivity with respect to PSD variation, there is no other data to show the method's' discriminating ability towards (b) (4) manufacturing conditions and any other critical quality attributes of the drug product. Additionally, despite the significant impact of API PSD on bioavailability, only a single tier limit of D90 – NMT (b) (4)u is proposed*

*Therefore, the following **IR was sent out** to the Applicant on 07/04/2019: Provide in your submission the dissolution method development report supporting the selection of the proposed commercial dissolution test (method D) evaluating the proposed drug product. Include the following information in the dissolution method development report*

a. *Rational why 60 rpm was selected and not* (b) (4) *rpm?*
b. *Why 0.2% CTAB was used and not lower concentration of the surfactant?*
c. *Data supporting the discriminating ability of the selected dissolution method. In general, ensure that the testing conducted to demonstrate the discriminating ability of the selected dissolution method compares the dissolution profiles of the reference (target) drug product and the test products that are intentionally manufactured with meaningful variations for the most relevant critical material attributes* (b) (4) *in the drug product), critical formulation variables, and critical process parameters (e.g.,* ± (b) (4) *% change to the specified values or ranges for these variables). Submit the dissolution profile data and similarity testing results obtained with appropriate statistical test (e.g., f2 values) comparing the test and reference drug products. In addition, if available, submit data showing that the selected dissolution method is able to reject product that is not bioequivalent to the reference-target drug product.*
d. *A list of the critical material attributes (CMAs) and critical process parameters (CPPs) affecting dissolution*

The Applicant's Response: The Applicant Responded[1] on July 17th, 2019. The Applicant submitted dissolution data using (b) (4) therefore 0.2% was selected. Additional data to support the method's discriminating capability was submitted. The method has fair discriminating capability with respect to particle size distribution. Additional (b) (4) The following additional data to support the method's discriminating capability was submitted (on July 17th, 2019) in response to FDA's IR#1 request.

[1] \\cdsesub1\evsprod\NDA212887\0013\m1\us\111-information-amendments

(b) (4)

Reference 172405897 (30/(b) (4) versus	No. of timepoints used for calculation	f_1 [1]	f_2 [2]	Profiles Equivalent?
152388107 (30/(b) (4)	3	1.7	91.9	Yes
152388108 (30/(b) (4)	3	17.0	55.0	No
162401103 (30/(b) (4) (b) (4)	3	8.3	69.1	Yes

***Reviewer's Final Evaluation**: The Applicant's response is satisfactory. Dissolution data and additional rational provided further supports their proposed dissolution method.* (b) (4) *Acceptable.*

Dissolution Acceptance criterion:

The Applicant proposed a dissolution acceptance criterion of Q=(b) (4)% at 25 minutes. The following IR was sent out:

***IR#2 dated 07/04/2019:** Clarify if the Phase III stability batch (GSK1265748) data were obtained using dissolution method C or D. Explain why a limit of Q (b) (4)% in (b) (4) min was used whereas the proposed dissolution acceptance criterion is Q=(b) (4)% in 25 min. Provide dissolution data (mean, individual, n=12, full profile, 5, 10, 15, 20, 30, 45, and 60 minutes) for the Phase III stability batch (b) (4) and/or any other clinical batches using the proposed dissolution method D.*

Applicant's Response[2] dated July 17th, 2019.

The Applicant clarified that the Phase 3 clinical batch is 152394829, [redacted] Dissolution data for the Phase 3 clinical batch (batch152394829) were obtained using dissolution method D. An acceptance criterion of Q = [redacted]% at [redacted] minutes was applied, which was the clinical specification in place at the time of testing. The Phase 3 batch also meets the proposed commercial acceptance criterion of Q = [redacted]% at 25 minutes after storage at 30°C/75% RH for 12 months and at 40°C/75% RH for 6 months. The stability data can be accessed via the following link:

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***Reviewer's Final Evaluation**: The Applicant's response is satisfactory. The provided dissolution data further supports the proposed dissolution acceptance criterion of Q= [redacted]% at 25 minutes. **Acceptable**.*

B.3 CLINICAL RELEVANCE OF DISSOLUTION METHOD & ACCEPTANCE CRITERIA *(e.g., IVIVR, IVIVC, In Silico Modeling, small scale in vivo)*

The Applicant attempted to show an in vitro-in vivo relationship (IVIVR) or in vitro-in vivo correlation (IVIVC), however, the relationship was not validated and was not shown to be predictive, therefore; an IVIVR/IVIVC was not established. The IVIVR cannot be used to support future CMC changes.

[2] \\cdsesub1\evsprod\NDA212887\0013\m1\us\111-information-amendments

B.12 BRIDGING OF FORMULATIONS

The following table includes the formulation composition used for the pivotal clinical trials batches and the primary stability batches:

Table 5. Proposed Commercial Formulation, also used in Pivotal Clinical Trials/Primary Stability Studies

Component	Quantity (mg/tablet)	Function	Reference to Standard
(b) (4)			
Cabotegravir Sodium, (b) (4)	31.62	Active	(b) (4)
Lactose Monohydrate	(b) (4)		USP/NF and Ph. Eur.
Microcrystalline Cellulose			USP/NF and Ph. Eur.
Hypromellose			USP/NF and Ph. Eur.
Sodium Starch Glycolate			USP/NF and Ph. Eur.
(b) (4)			
Magnesium Stearate	(b) (4)		USP/NF and Ph. Eur.
(b) (4)	-	-	-
Film Coat			
(b) (4)			
Film Coated Tablet Weight	515.00	-	-

Notes:

1. Equivalent to 30 mg of cabotegravir (free acid). Actual amount may vary based on purity of drug substance
2. (b) (4)
3.
4.

Assessment: *Adequate*

As noted in the above formulation composition (foot note # 4), the phase 3 clinical batches only used (b) (4) *formulation. The applicant claimed that they both have the same quantitative and qualitative formula. However, while the qualitative and quantitative*

(b) (4)

Reviewer's assessment: Bridging is not need because the clinical trial drug product batch has the same formulation composition, manufacturing site, and image as the proposed commercial drug product. **Acceptable**

B. 13 BIOWAIVER REQUEST

Assessment: *None*

R. REGIONAL INFORMATION

Comparability Protocols

Assessment: *None*

Post-Approval Commitments

Assessment: *None*

Lifecycle Management Considerations

The drug appears to be a BCS class II drug. Any change in the API (b) (4) *and drug product manufacturing process may impact oral bioavailability. The Applicant should submit a prior approval supplement for any such changes during the lifecycle of the drug product.*

[3] \\cdsesub1\evsprod\NDA212887\0001\m3\32-body-data\32p-drug-prod\cabotegravir-tablet\32p4-contr-excip\noncompendial-opadry

[4] \\cdsesub1\evsprod\NDA212887\0001\m3\32-body-data\32p-drug-prod\cabotegravir-tablet\32p4-contr-excip\noncompendial-aquarius

BIOPHARMACEUTICS LIST OF DEFICIENCIES

None

Primary Biopharmaceutics Assessor's Name and Date:
Akm Khairuzzaman, Ph.D., 8/14/2019

Secondary Assessor Name and Date:
Elsbeth Chikhale, Ph.D., 8/23/2019

Akm Khairuzzaman

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Elsbeth Chikhale

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CHAPTER III: ENVIRONMENTAL

IQA NDA Assessment Guide Reference

R REGIONAL INFORMATION

Environmental Analysis

Application: NDA 212887

Drug product: VOCABRIA (cabotegravir sodium) tablets, for oral use. Cabotegravir is a human immunodeficiency virus type-1 (HIV-1) integrase strand transfer inhibitor (INSTI).

Indication: indicated in combination with EDURANT (rilpivirine) for short-term treatment of HIV-1 infection in adults who are virologically suppressed (HIV-1 RNA less than 50 copies/mL) and who have no known or suspected resistance to either cabotegravir or rilpivirine, for use as:

- oral lead-in to assess the tolerability of cabotegravir prior to administration of long-acting CABENUVA (cabotegravir; rilpivirine) extended-release injectable suspensions.
- oral therapy for patients who will miss planned injection dosing with CABENUVA injectable suspensions.

Proposed dose: One tablet of VOCABRIA 30 mg taken orally once daily for approximately 1 month in combination with one tablet of EDURANT 25 mg taken orally once daily.

Claim of Categorical Exclusion: The applicant has submitted a claim of categorical exclusion under 21 CFR 25.31(b) and a statement of no extraordinary circumstances under 21 CFR 25.21. Environmental concentration are estimated. Environmental effects studies were not submitted by the applicant.

Reviewer's Assessment: Adequate

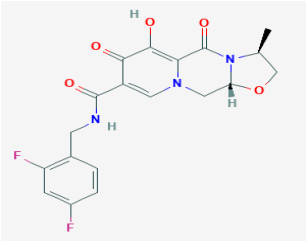
The applicant's claim of categorical exclusion (21 CFR 25.31(b)) and provided statement of no extraordinary circumstance are acceptable.

QSAR modelling for estrogen receptor (ER) and androgen receptor (AR) activity indicates a low potential for cabotegravir sodium interaction with estrogen and androgen receptors. Animal (rat, rabbit) studies indicate low potential for teratogenicity at mg/kg levels. Modeled aquatic toxicity results show a large margin between exposure concentrations and effects. The Fish Plasma Model output indicates that additional chronic studies may be required for NDA supplements that increase use significantly. Based on low potential for cabotegravir sodium interaction with estrogen and androgen receptors, low environmental concentrations of cabotegravir sodium (EIC = (b) (4) µg/L EEC = (b) (4) µg/L), and exposure/effects ratios, significant environmental impacts are not expected due to approval of this application.

Application Review

- Production volume estimate = (b) (4) kg/year (conservative estimate considering that (b) (4)% of the HIV-positive population in the US would take the drug)
- Expected Introduction Concentration (EIC) = (b) (4) µg/L; EEC = (b) (4) µg/L

- Log Kow = (b) (4)
- BCF_{fish} = (b) (4)
- EC_{fish} = (b) (4) µg/L
- Cmax (Human therapeutic concentration; month 3 onward following 400 mg monthly IM dose) = (b) (4) µg/mL = (b) (4) µg/L



FISH PLASMA MODEL (Human therapeutic concentration)

Source	C_{max} (Human Therapeutic Conc) (µg/mL)	C_{max} (Human Therapeutic Conc) (µg/L)	EC_{fish} (µg/L)	Effect ratio
Module 2.6.1. Intro	(b) (4)	(b) (4)	(b) (4)	(b) (4)

Effect ratio = EC_{fish}/C_{max}

Fish plasma model result (ER< (b) (4)) indicate fish chronic studies may be needed.

AQUATIC TOXICOLOGY MODEL PREDICTIONS

1. Aquatic Toxicity predictions (Danish QSAR DB)
    - Aquatic toxicity predictions for cabotegravir are not reported in the Danish QSAR toolbox database. Data for top 4 analogues were retrieved. All four analogues have similarity index of (b) (4)
    - Fathead minnow: 96h LC_{50} estimated to range from (b) (4) mg/L= (b) (4) µg/L
    - *Daphnia magnia*: 48h EC_{50} estimated to range from (b) (4) mg/L= (b) (4) µg/L
    - *Pseudokirchneriella s*.: 72h EC_{50} estimated to range from (b) (4) mg/L= (b) (4) µg/L
    - *Pseudokirchneriella* is predicted to be most sensitive organism based on analogue data.
    - The lowest predicted acute toxicity value (b) (4) µg/L) is ~ 14-fold higher than the EIC (b) (4) µg/L).

2. ECOSAR
    - QSAR predictions for acute and chronic effects
    - Functional groups: aliphatic amines, vinyl/allyl/propargyl ketones, acrylamides, vinyl allyl/propargyl alcohols-unhindered

    2.1 ACUTE TOXICITY

    - Lowest predicted acute toxicity values for fish (LC_{50}_96h): (b) (4) mg/L = (b) (4) µg/L
    - Lowest predicted acute toxicity values for Daphnid (LC_{50}_48h): (b) (4) mg/L = (b) (4) µg/L
    - Lowest predicted acute toxicity values for green algae (EC_{50}_96h): (b) (4) mg/L= (b) (4) µg/L

- Lowest predicted acute toxicity value for most sensitive organism (algae) is > (b) (4) -fold higher than the EIC.

2.2 CHRONIC TOXICITY

- Lowest predicted chronic toxicity values for fish: (b) (4) mg/L = (b) (4) µg/L
- Lowest predicted chronic toxicity values for Daphnid: (b) (4) mg/L = (b) (4) µg/L
- Lowest predicted chronic toxicity values for green algae: (b) (4) mg/L = (b) (4) µg/L
- Lowest predicted chronic toxicity value for most sensitive organism (green algae) is ≥ (b) (4) -fold higher than the EIC.

3. QSARs for estrogen receptor (ER) and androgen receptor (AR) activity:
   - Predictions for ER activity NOT reported in Mansouri et al., 2016 (CERAPP)
   - ER models: INACTIVE in ER binding, agonist, and antagonist models (OCHEM models)
   - AR models: INACTIVE in AR binding, agonist, and antagonist models (OCHEM models)

NONCLINICAL TOXICOLOGY

- Carcinogenesis: Cabotegravir was not carcinogenic in long-term studies in the mouse and rat.
- Mutagenesis: Cabotegravir was not genotoxic in the bacterial reverse mutation assay, mouse lymphoma assay, or in the *in vivo* rodent micronucleus assay.
- Impairment of Fertility: No human data on the effect of cabotegravir on fertility are available. Cabotegravir, when administered orally to male and female rats at 1,000 mg/kg/day (exposure [AUC] >30 times the exposure in humans at the oral MRHD of 30 mg) for up to 26 weeks, did not cause adverse effects on male or female reproductive organs or spermatogenesis. No functional effects on mating or fertility were observed in male or female rats when administered cabotegravir at doses up to 1,000 mg/kg/day.

EXCRETION

Major route of elimination: Metabolism

- % of dose excreted as total ^{14}C (unchanged drug) in urine: 27
- % of dose excreted as total ^{14}C (unchanged drug) in feces: 59

Primary Environmental Assessor Name and Date:

Secondary Assessor Name and Date (and Secondary Summary, as needed):

Raanan Bloom

Digitally signed by Raanan Bloom
Date: 10/24/2019 12:57:25PM
GUID: 508da72a0002a6d1071f3297897e4f1f

Michael Furness

Digitally signed by Michael Furness
Date: 10/24/2019 01:00:47PM
GUID: 502e8c7600003dd8331cf6eebf43697a

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

ERIKA E ENGLUND
11/07/2019 06:11:29 PM

U.S. FOOD & DRUG ADMINISTRATION

RECOMMENDATION

☒ Approval
☐ Approval with Post-Marketing Commitment
☐ Complete Response

NDA 212888
Assessment # 2

Drug Product Name	CABENUVA (cabotegravir extended-release injectable suspension; rilpivirine extended-release injectable suspension)
Dosage Form	extended release injectable suspension
Strength	400 mg/600 mg & 600 mg/900 mg Dosing Kit
Route of Administration	IM
Rx/OTC Dispensed	Rx
Applicant	Viiv Healthcare Company
US agent, if applicable	NA

Submission(s) Assessed	Document Date	Discipline(s) Affected
eCTD 0054	07/28/2020	Resubmitted NDA
eCTD 0055	08/25/2020	Quality
eCTD 0056	11/06/2020	Quality
eCTD 0058	12/03/2020	Quality

QUALITY ASSESSMENT TEAM

Discipline	Primary Assessment	Secondary Assessment
Drug Substance	Kabir Shahjahan	Haripada Sarker
Drug Product	Peter Guerrieri	Erika Englund
Manufacturing	Hang Guo	Pei-I Chu
Microbiology	NA	NA
Biopharmaceutics	Gerlie Gieser	Elsbeth Chikhale
Regulatory Business Process Manager	Shamika Brooks and Anh-Thy Ly	
Application Technical Lead	Erika Englund	
Laboratory (OTR)	NA	
Environmental	NA	

QUALITY ASSESSMENT DATA SHEET

IQA NDA Assessment Guide Reference

1. RELATED/SUPPORTING DOCUMENTS: Refer to CMC Review #1

EXECUTIVE SUMMARY

IQA NDA Assessment Guide Reference

I. RECOMMENDATIONS AND CONCLUSION ON APPROVABILITY

The NDA, as amended, has provided adequate CMC information to assure the identity, strength, purity, and quality of the proposed drug product. Therefore, this NDA is recommended for approval by the Office of Pharmaceutical Quality (OPQ) at this time. The manufacturing and testing facilities for this NDA are deemed acceptable and an overall "Approve" recommendation was entered into Panorama 12/15/2020.

II. SUMMARY OF QUALITY ASSESSMENTS

A. Product Overview

The proposed product is a kit containing two separate vialed extended release injectable products: one vial contains cabotegravir, and the second vial contains the rilpivirine free base. Both vials contain suspensions of the drug substance in (b) (4) solution of excipients. The kits are indicated for the treatment of HIV-1 and would be administered IM once monthly. The applicant proposes marketing two dosage strengths of the kits designed to administer either 2 ml (400 mg/600 mg kit) or 3 ml (600 mg/900 mg kit) of each product. The combination product co-packs contain:

400 mg/600 mg Kit:

- single-dose vial of 400 mg/2 ml of cabotegravir
- single-dose vial of 600 mg/2 ml of rilpivirine

600 mg/900 mg Kit:

- single-dose vial of 600 mg/3 ml of cabotegravir
- single-dose vial of 900 mg/3 ml of rilpivirine

Drug products for each of the two fill presentations are co-packaged with the following aspiration and dosing devices:

- two sterile, single-use vial adaptors
- two 5-mL sterile, single-use syringes
- two sterile, single-use 23 gauge, 1.5-inch safety needles

NDA 212887 is concurrently under review, and describes cabotegravir tablets as an oral lead-in for the extended release injectable suspensions described in this NDA. Refer to CMC Review #1 for a complete description of the products.

This NDA was recommended for a Complete Response (CR) from a CMC perspective in CMC Review #1 dated 11/26/2019. The CR letter on 12/19/2019 included 3 CMC deficiencies concerning the inspectional issues at Glaxo Operations UK Limited, a greater quantity of (b) (4) and the inadequate DMF (b) (4) In addition to these 3 deficiencies, the CR letter included 3 CMC comments concerning the upper limit for the drug product particle size acceptance criteria, a request for the full details of (b) (4) described in the December 17, 2019 submission.

A type A meeting was held on March 24, 2020 to discuss plans to address the product quality and facility issues in NDA 212888, and the NDA was resubmitted with a Complete Response on 7/28/2020. This NDA is currently recommended for approval from a CMC perspective.

Proposed Indication(s) including Intended Patient Population	Treatment of HIV-1 in adults
Duration of Treatment	Chronic
Maximum Daily Dose	600 mg cabotegravir and 900 mg of rilpivirine
Alternative Methods of Administration	None.

B. Quality Assessment Overview

Drug Substance: Adequate

This NDA was recommended for approval from a Drug Substance perspective in CMC Review #1. The drug substance information for cabotegravir is contained in NDA 212888, and the drug substance information for rilpivirine is referenced to DMF (b) (4). The drug substance information for cabotegravir remains unchanged from CMC Review #1. Additional information for rilpivirine had been submitted to the DMF since

CMC Review #1. The drug substance information for rilpivirine in DMF (b) (4) was found adequate to support this NDA on 11/06/2020.

This NDA is recommended for approval from a drug substance perspective. For additional details, refer to the review by Kabir Shahjahan, Ph.D.

Drug Product: Adequate

The drug product review recommended the NDA for approval in CMC Review #1. The drug product information for the rilpivirine injectable suspension was referenced to DMF (b) (4). This DMF was found adequate to support the NDA in CMC Review # 1 (DMF review dated 10/31/2019). The DMF updates since CMC Review #1 were evaluated and the DMF was found adequate to support the NDA again on 12/15/2020.

The CMC information for cabotegravir injectable suspension was included in the NDA. In the CR letter, one of the CMC comments included a request for additional justification for the upper limit for the median drug product particle size. Following discussion with the Biopharmaceutics and Clinical Pharmacology teams, this upper limit was found acceptable (refer to biopharmaceutics review also for additional discussion). The drug product specification was previously found acceptable in CMC Review #1, and no changes to the tests or acceptance criteria were necessary based on this discussion.

(b) (4)

months of stability data for 3 process qualification batches at the proposed commercial scale were submitted, and the stability studies with these batches will be continued. All results were within specification and the data was acceptable.

This NDA is recommended for approval from a drug product perspective. For additional details, refer to the review by Pete Guerrieri, Ph.D.

Labeling: Adequate

Labeling recommendations were communicated to the OND PM.

Manufacturing: Adequate

This NDA was recommended for a CR from an OPMA perspective in CMC Review #1. The first deficiency in the CR letter dated 12/19/2019 concerned the pre-approval inspection of Glaxo Operations UK Limited. In this review cycle, an RAI was sent to the facility on 9/28/2020, and the responses were acceptable to down grade the site from OAI to VAI. An Overall Manufacturing Inspection Recommendation was entered into Panorama as “Approve” on 12/15/2020.

The second deficiency in the CR letter concerned the results from the (b) (4)

testing, and manufactured three additional commercial scale PQ batches. The totality of evidence shows that there exists enough process understanding and in-process controls to mitigate the risk of (b) (4)

The third deficiency in the CR letter concerned the inadequate status of DMF (b) (4). This DMF was found adequate from an OPMA perspective on 12/15/2020. In addition, this DMF was found adequate to support the NDA from a drug product perspective (see discussion above).

The responses to the deficiencies in the CR letter were adequate, and this NDA is recommended for approval from an OPMA perspective. For additional details, refer to the review by Hang Guo, Ph.D.

Biopharmaceutics: Adequate

This NDA was recommended for approval from a Biopharmaceutics perspective in CMC Review #1. For the NDA resubmission, a

Biopharmaceutics memo documented the internal communications between the Drug Product, Biopharmaceutics, and Clinical Pharmacology review disciplines as related to the FDA assessment of the influence of cabotegravir median particle size on in vivo PK of cabotegravir following administration as an intramuscular injection in healthy subjects. Based on email communications among the review disciplines, it is concluded that from the Biopharmaceutics perspective, the Applicant's proposed cabotegravir X50 upper tolerance limit of "NMT (b) (4)" is reasonable.

This NDA is recommended for approval from a Biopharmaceutics perspective. For additional details, refer to the review by Gerlie Gieser, Ph.D.

Microbiology (if applicable): Adequate

NA. The NDA was recommended for approval from a Microbiology perspective in CMC Review #1. The NDA resubmission did not contain information related to microbiology, and No Action was Indicated in Panorama.

D. List of Deficiencies for Complete Response

1. Overall Quality Deficiencies (Deficiencies that affect multiple sub-disciplines)

None

2. Drug Substance Deficiencies

3. Drug Product Deficiencies

4. Labeling Deficiencies

5. Manufacturing Deficiencies

6. Biopharmaceutics Deficiencies

7. Microbiology Deficiencies

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CHAPTER IV: LABELING

IQA NDA Assessment Guide Reference

This labeling review was adequate in review #1. Minor updates were provided in the submission below following the CR letter for the original submission. The updates are included in this review.

Document(s) Assessed	Date Received
0054 (58) Resubmission	**07/28/2020**

1.0 PRESCRIBING INFORMATION

Assessment of Product Quality Related Aspects of the Prescribing Information:

1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION

Item	Information Provided in the NDA	Assessor's Comments
Product Title in Highlights		
Proprietary name	CABENUVA	Adequate.
Established name(s)	cabotegravir extended-release injectable suspension; rilpivirine extended-release injectable suspension), co-packaged for intramuscular use	Adequate.
Route(s) of administration	Intramuscular	Adequate.
Dosage Forms and Strengths Heading in Highlights		
Summary of the dosage form(s) and strength(s) in metric system.	Cabotegravir extended-release injectable suspension and rilpivirine extended-release injectable suspension, co-packaged as follows: (3) CABENUVA 400-mg/600-mg Kit: • single-dose vial of 400 mg/2 mL (200 mg/mL) cabotegravir • single-dose vial of 600 mg/2 mL (300 mg/mL) rilpivirine CABENUVA 600-mg/900-mg Kit: • single-dose vial of 600 mg/3 mL (200 mg/mL) cabotegravir	Adequate.

	• single-dose vial of 900 mg/3 mL (300 mg/mL) rilpivirine	
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	Single-dose	Adequate.

1.2 FULL PRESCRIBING INFORMATION

1.2.1 Section 2 (DOSAGE AND ADMINISTRATION)

Item	Information Provided in the NDA	Assessor's Comments
DOSAGE AND ADMINISTRATION section		
Special instructions for product preparation (e.g., reconstitution and resulting concentration, dilution, compatible diluents, storage conditions needed to maintain the stability of the reconstituted or diluted product)	Refer to the Instructions for Use for complete administration instructions with illustrations. A complete dose requires 2 injections: one injection of cabotegravir and one injection of rilpivirine [see Dosage and Administration (2.3)]. Cabotegravir and rilpivirine are suspensions for gluteal intramuscular injection that do not need further dilution or reconstitution. Before preparing the injections, remove CABENUVA from the refrigerator and wait at least 15 minutes to allow the medicines to come to room temperature. The vials may remain in the carton at room temperature for up to 6 hours. If not used within 6 hours, the medication must be discarded. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. The cabotegravir vial has a brown tint to the glass which may limit visual inspection. Discard CABENUVA if either medicine exhibits particulate matter or discoloration. Shake each vial of CABENUVA vigorously so that the suspensions look uniform before injecting. Small air bubbles are expected and acceptable. Once the suspensions have been drawn into the respective syringes, the injections should be administered as soon as possible, but may remain in the syringes for up to 2 hours. If 2 hours are exceeded, the medication, syringes, and needles must be discarded [see How Supplied/Storage and Handling (16)].	Adequate. The in-use conditions are supported by in-use stability results.

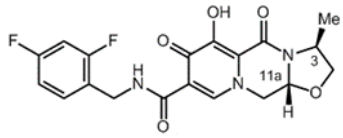
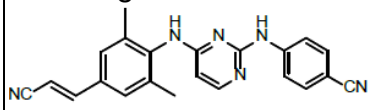
1.2.2 Section 3 (DOSAGE FORMS AND STRENGTHS)

Item	Information Provided in the NDA	Assessor's Comments
DOSAGE FORMS AND STRENGTHS section		
Available dosage form(s)	CABENUVA contains a single-dose vial of cabotegravir as a white to light pink, free-flowing extended-release injectable suspension and a single-dose vial of rilpivirine as a white to off-white extended-release injectable suspension, co-packaged as follows: CABENUVA 400-mg/600-mg Kit • Injection: 400 mg/2 mL (200 mg/mL) of cabotegravir suspension in single-dose vial • Injection: 600 mg/2 mL (300 mg/mL) of rilpivirine suspension in single-dose vial CABENUVA 600-mg/900-mg Kit • Injection: 600 mg/3 mL (200 mg/mL) of cabotegravir suspension in single-dose vial • Injection: 900 mg/3 mL (300 mg/mL) of rilpivirine suspension in single-dose vial	Adequate.
Strength(s) in metric system	See above.	Adequate.
If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance	N/A	
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting	See above.	Adequate.
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	

For injectable drug products for parental administration, use appropriate labeling term (e.g., single-dose, multiple-dose, single-patient-use). Other package type terms include pharmacy bulk package and imaging bulk package.	Single-dose	Adequate.

1.2.3 Section 11 (DESCRIPTION)

Item	Information Provided in the NDA	Assessor's Comments
DESCRIPTION section		
Proprietary and established name(s)	CABENUVA, cabotegravir extended-release injectable suspension; rilpivirine extended-release injectable suspension), co-packaged for intramuscular use	Adequate.
Dosage form(s) and route(s) of administration	Injectable suspension for intramuscular injection	Adequate.
If the active ingredient is a salt, apply the USP Salt Policy and include the equivalency statement per FDA Guidance.	N/A	
List names of all inactive ingredients. Use USP/NF names. Avoid Brand names.	Cabotegravir ER injectable suspension: mannitol (35 mg/mL), polyethylene 520 glycol (PEG) 3350 (20 mg/mL), polysorbate 20 (20 mg/mL), and Water for Injection Rilpivirine ER injectable suspension: citric acid monohydrate (1 mg/mL), poloxamer 338 (50 mg/mL), Water for Injection, glucose monohydrate to ensure isotonicity, and sodium dihydrogen phosphate monohydrate and sodium hydroxide to adjust pH	Adequate.
For parenteral injectable dosage forms, include the name and quantities of all inactive ingredients. For ingredients added to adjust the pH or make isotonic, include the name and statement of effect.	See above	Adequate.

If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	N/A	
Statement of being sterile (if applicable)	Yes	Adequate.
Pharmacological/ therapeutic class	Cabotegravir: HIV INSTI Rilpivirine: HIV NNRTI	Adequate.
Chemical name, structural formula, molecular weight	Cabotegravir: The chemical name for cabotegravir is (*3S,11aR*)-N-[(2,4-difluorophenyl)methyl]-6-hydroxy-3-methyl-5,7-dioxo-2,3,5,7,11,11a-hexahydro[1,3]oxazolo[3,2-a]pyrido[1,2-d]pyrazine-8-carboxamide.The empirical formula is $C_{19}H_{17}F_2N_3O_5$ and the molecular weight is 405.35 g/mol. It has the following structural formula:  Rilpivirine: The chemical name for rilpivirine is 4-[[4-[[4-[(E)-2-cyanoethenyl]-2,6-dimethylphenyl]amino]-2-pyrimidinyl]amino]benzonitrile. Its molecular formula is $C_{22}H_{18}N_6$ and its molecular weight is 366.42. Rilpivirine has the following structural formula: 	Adequate.
If radioactive, statement of important nuclear characteristics.	N/A	
Other important chemical or physical properties (such as pKa or pH)	N/A	

Section 11 (DESCRIPTION) Continued

Item	Information Provided in the NDA	Assessor's Comments
For oral prescription drug products, include gluten statement if applicable	N/A	
Remove statements that may be misleading or promotional (e.g., "synthesized and developed by Drug Company X," "structurally unique molecular entity"	N/A	

1.2.4 Section 16 (HOW SUPPLIED/STORAGE AND HANDLING)

Item	Information Provided in the NDA	Assessor's Comments
HOW SUPPLIED/STORAGE AND HANDLING section		
Available dosage form(s)	CABENUVA is supplied in 2 dosing kits. Each kit contains one vial of cabotegravir extended-release injectable suspension and one vial of rilpivirine extended-release injectable suspension, co packaged as follows: CABENUVA 400-mg/600-mg Kit (NDC 49702-253-15) containing: • One single-dose vial of cabotegravir extended-release injectable suspension containing 400 mg/2 mL (200 mg/mL) of cabotegravir. • One single-dose vial of rilpivirine extended-release injectable suspension containing 600 mg/2 mL (300 mg/mL) of rilpivirine CABENUVA 600-mg/900-mg Kit (NDC 49702-240-15) containing: • One single-dose vial of cabotegravir extended-release injectable suspension containing 600 mg/3 mL (200 mg/mL) of cabotegravir. • One single-dose vial of rilpivirine extended-release injectable suspension containing 900 mg/3 mL (300 mg/mL) of rilpivirine. Each dosing kit also contains 2 syringes, 2 syringe labels, 2 vial adapters, and 2 needles for intramuscular injection (23-gauge, 1½ inch). The vial stoppers are not made with natural rubber latex.	Adequate.
Strength(s) in metric system	Yes; see above.	Adequate.
Available units (e.g., bottles of 100 tablets)	See above.	Adequate.
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	Yes; see above.	Adequate.

Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state “functionally scored”	N/A	
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	Single-dose	Adequate.

Section 16 (HOW SUPPLIED/STORAGE AND HANDLING) (Continued)

Item	Information Provided in the NDA	Assessor’s Comments

Special handling about the supplied product (e.g., protect from light, refrigerate). If there is a statement to “Dispense in original container,” provide reason why (e.g. to protect from light or moisture, to maintain stability, etc.)	Store CABENUVA in the refrigerator at 2°C to 8°C (36°F to 46°F) in the original carton until ready to use. Do not freeze. Do not mix with any other product or diluent. Prior to administration, vials should be brought to room temperature (not to exceed 25°C [77°F]). Vials may remain in the carton at room temperature for up to 6 hours. If not used after 6 hours, they must be discarded. Once the suspensions have been drawn into the respective syringes, the injections should be administered as soon as possible, but may remain in the syringe for up to 2 hours. If 2 hours are exceeded, the medication, syringes, and needles must be discarded.	Adequate. The shelf life and in-use conditions are supported by stability results.
If the product contains a desiccant, ensure the size and shape differ from the dosage form and desiccant has a warning such as “Do not eat.”	N/A	
Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature.	2°C to 8°C (36°F to 46°F)	Adequate.
Latex: If product does not contain latex and manufacturing of product and container did not include use of natural rubber latex or synthetic derivatives of natural rubber latex, state: “Not made with natural rubber latex. Avoid statements such as “latex-free.”	The vial stoppers are not made with natural rubber latex.	Adequate.

Include information about child-resistant packaging	N/A	

1.2.5 Other Sections of Labeling
N/A

1.2.6 Manufacturing Information After Section 17 (for drug products)

Item	Information Provided in the NDA	Assessor's Comments
Manufacturing Information After Section 17		
Name and location of business (street address, city, state and zip code) of the manufacturer, distributor, and/or packer	GlaxoSmithKline Research Triangle Park, NC 27709	Adequate.

2.0 PATIENT LABELING

Assessment of Product Quality Related Aspects of Patient Labeling (e.g., Medication Guide, Patient Information, Instructions for Use):
The product is to be administered by healthcare professionals only. The IFU was reviewed by DMEPA.

3.0 CARTON AND CONTAINER LABELING

3.1 Container Label
See section 1.14

3.2 Carton Labeling
See section 1.14

Item	Information Provided in the NDA	Assessor's Comments about Carton Labeling
Proprietary name, established name, and dosage form (font size and prominence)	CABENUVA, Cabotegravir extended-release injectable suspension, 400 mg/2 mL (200 mg/mL) co-packaged with Rilpivirine extended-release injectable suspension, 600 mg/2 mL (300 mg/mL)	Adequate. The language on the left is for the 400 mg/600 mg Kit. The language for 600 mg/900 mg Kit is identical with the exception of the dose strengths.
Dosage strength	400-mg/600-mg Kit (NDC 49702-253-15): Cabotegravir - 400 mg/2 mL (200 mg/mL); Rilpivirine – 600 mg/2 mL (300 mg/mL) 600-mg/900-mg Kit (NDC 49702-240-15) Cabotegravir - 400 mg/2 mL (200 mg/mL); Rilpivirine – 600 mg/2 mL (300 mg/mL)	Adequate.
Route of administration	For gluteal intramuscular use only.	Adequate.
If the active ingredient is a salt, include the equivalency statement per FDA Guidance	N/A	
Net contents (e.g. tablet count)	-1 cabotegravir single-dose vial -1 rilpivirine single-dose vial -2 vial adapters -2 syringes -2 injection needles (23 gauge, 1½ inch) -2 syringe labels -Prescribing information -Patient information -Instructions for use	Adequate.
"Rx only" displayed on the principal display	Yes	Adequate.
NDC number	Yes, see above	Adequate.
Lot number and expiration date	Yes	Adequate.

Storage conditions. If applicable, include a space on the carton labeling for the user to write the new BUD.	Store in refrigerator at 2°C to 8°C (36°F to 46°F). Do not freeze. Discard unused portion.	Adequate.
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use)	Single-dose vial	Adequate.
Other package terms include pharmacy bulk package and imaging bulk package which require “Not for direct infusion” statement.	N/A	
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	N/A	
Bar code	Yes	Adequate.

Item	Information Provided in the NDA	Assessor's Comments about Carton Labeling
Name of manufacturer/distributor	Manufactured for: Viiv Healthcare Research Triangle Park, NC 27709 By: GlaxoSmithKline Research Triangle Park, NC 27709 (b) (4)	Adequate.
Medication Guide (if applicable)	N/A	
No text on Ferrule and Cap overseal	Yes	Adequate.
When a drug product differs from the relevant USP standard of strength, quality, or purity, as determined by the application of the tests, procedures, and acceptance criteria set forth in the relevant compendium, its difference shall be plainly stated on its label.	N/A	
And others, if space is available	N/A	

Assessment of Carton and Container Labeling: Adequate.

ITEMS FOR ADDITIONAL ASSESSMENT

N/A

Overall Assessment and Recommendation:

Based on this labeling review, the sections herein are adequate for approval.

Primary Labeling Assessor Name and Date:

Pete Guerrieri, PhD, Branch 2; Division of New Drug Product I.

Secondary Assessor Name and Date (and Secondary Summary, as needed):

Peter Guerrieri

Digitally signed by Peter Guerrieri
Date: 12/14/2020 10:09:08PM
GUID: 54eb8ba100062ea99cbaab7c64143df3

Erika Englund

Digitally signed by Erika Englund
Date: 12/16/2020 09:54:32AM
GUID: 51389ea30003450414230afb8c3e8114

BIOPHARMACEUTICS MEMORANDUM TO FILE	
NDA Number	212888 (SN-0054)
Type of Submission	NDA Resubmission (Class 2)
Drug Product/ **Route of Administration**	Cabotegravir Extended-Release (ER) Injectable Suspension, 200 mg/mL (co-packaged with Rilpivirine ER Injectable Suspension, 300 mg/mL); For intramuscular injection
Applicant/Sponsor	ViiV Healthcare Company
Consult Request Date	9/16/2020
Date of Memo	9/17/2020
Biopharmaceutics Consult Reviewers	Gerlie Gieser, Ph.D. (primary) Elsbeth Chikhale, Ph.D. (secondary)

EXECUTIVE SUMMARY:

This Biopharmaceutics memo documents the internal communications between the Drug Product, Biopharmaceutics, and Clinical Pharmacology review disciplines as related to the FDA assessment of the influence of cabotegravir median particle size on *in vivo* PK of cabotegravir following administration as an intramuscular injection in healthy subjects. Based on email communications among the review disciplines, it is concluded that from the Biopharmaceutics perspective, the Applicant's proposed cabotegravir X_{50} upper tolerance limit of "NMT (b) (4)" is reasonable.

BIOPHARMACEUTICS CONSULT REVIEW:

Background:

On 9/16/2020, Dr. Peter Guerreri (the Drug Product Reviewer assigned to NDA 212888 Resubmission) requested the assigned Biopharmaceutics Consult Reviewer to assess the PK data of Relative Bioavailability Study LAI116815 because this PK study was referenced by the Applicant in the scientific justification for the proposed cabotegravir X_{50} tolerance limit. For details regarding the PK data submitted by the Applicant to support the proposed drug substance particle size acceptance criterion, refer to pages 21 to 25 (of 73) of the 7/28/2020 Response to the FDA Quality Information Request[1]. Note that previously, Dr. Akm Khairuzzaman and Dr. Elsbeth Chikhale (the Biopharmaceutics Reviewers of the original NDA submission) determined the *in vitro* drug release method and acceptance criteria, extended release claim, and bridging information in the NDA to be adequate[2].

Biopharmaceutics Consult Reviewer Assessment/Recommendation/Conclusion:

On 9/17/2020, Dr. Gieser (the primary Biopharmaceutics Consult Reviewer) reminded Dr. Guerreri that the consult request pertaining to the impact of cabotegravir API particle size was addressed previously as part of the (March 2020) discussions pertaining to the FDA response to the Sponsor question in a Type A CMC meeting package under IND 109678 regarding the same issue. The Biopharmaceutics input at that time was as shown below; however, Dr. Guerreri indicated that it was not necessary to seek additional

[1] \\CDSESUB1\evsprod\nda212888\0054\m1\us\111-information-amendments\cmc-response-28jul2020.pdf
[2] https://panorama.fda.gov/document/view?ID=5da6599a004234a05d32a0a7c9b6d074

justification for the lower limit based on available data/information (see email attachment 1 in Appendix, and Type A CMC meeting minutes[3] dated 4/13/2020).

> *Considering the PK results of Relative BA Study LAI116815 (that compared drug products with X_{50} = NM (b) (4) and NM (b) (4) as well as the use/dosing of a drug product lot with X_{50} = (b) (4) in a Phase 3 clinical trial, the Sponsor's justification for the proposed X_{50} upper limit ((b) (4) is reasonable, from the Biopharmaceutics perspective. In the NDA Resubmission, the Applicant should include a similar justification for the proposed X_{50} lower limit of (b) (4) µm, especially because there is no additional earlier IVR specification time point(s) before "Q = (b) (4)% at (b) (4)min" for the proposed extended release/long-acting injection drug product.*

In response to Dr. Guerreri's follow up request, this Reviewer also provided the 3/18/2020 email communication from Dr. Mario Sampson (Clinical Pharmacology Reviewer) regarding his assessment that "from a statistical perspective, [he] agrees that the [cabotegravir] exposures [following 'NM (b) (4) versus 'NM (b) (4) are comparable in that none of the 90% CIs excluded a ratio of (b) (4)" (refer to email attachment 2 in Appendix).

Based on the internal FDA discussions regarding the results of the referenced PK study (as well as based on evidence of clinical use), this Biopharmaceutics Reviewer considers the Applicant's proposed X_{50} upper limit (NMT (b) (4) reasonable.

[3] https://darrts.fda.gov//darrts/faces/ViewDocument?documentId=090140af80556c71&_afrRedirect=1691565541439782

APPENDIX:

Email Communication 1 (Drug Product and Biopharmaceutics)

IND 109678 for cabotegravir (GSK12

Email Communication 2 (Biopharmaceutics and Clinical Pharmacology)

RE NDA 212888 for Cabotegravir Long-/

Gerlie Gieser

Digitally signed by Gerlie Gieser
Date: 9/29/2020 09:28:06AM
GUID: 507592ba00003d190b2ea34fe8fb8ccb

Elsbeth Chikhale

Digitally signed by Elsbeth Chikhale
Date: 9/29/2020 03:25:17PM
GUID: 50743ccc000031928b54eba1769a5df9

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

ERIKA E ENGLUND
12/18/2020 02:35:07 PM

U.S. FOOD & DRUG ADMINISTRATION

RECOMMENDATION

☐ Approval
☐ Approval with Post-Marketing Commitment
☒ Complete Response

NDA 212888
Assessment #1

Drug Product Name	CABENUVA (cabotegravir extended-release injectable suspension; rilpivirine extended-release injectable suspension)
Dosage Forms	extended release injectable suspension
Strength	400-mg/600-mg & 600mg/900mg Dosing Kit
Route of Administration	IM
Rx/OTC Dispensed	RX
Applicant	ViiV Healthcare Company

Submission(s) Assessed	Document Date	Discipline(s) Affected
Orig	4/29/2019	
Quality Response to IR	6/21/2019	Manufacturing
Quality Response to IR	7/17/2019	Drug product and Biopharmaceutics
Quality Response to IR	8/9/2019	Manufacturing/Facilities, Drug Product, Biopharmaceutics, Environmental Assessment
Quality Response to IR	8/19/2019	Microbiology
Quality Response to IR	8/30/2019	Drug Product
Quality Response to IR	9/16/2019	Drug Product
Quality Response to IR	9/25/2019	Microbiology
Quality Response to IR	9/27/2019	Microbiology
Quality Response to IR	10/7/2019	Manufacturing
Quality Response to IR	10/8/2019	Manufacturing
Quality Response to IR	10/15/2019	Microbiology
Quality Response to IR	10/21/2019	Drug Product
Quality Response to IR	10/31/2019	Manufacturing

QUALITY ASSESSMENT TEAM

Discipline	Primary Assessment	Secondary Assessment
Drug Substance	Kabir Shahjahan	Haripada Sarker
Drug Product	Peter Guerrieri	Balajee Shanmugam
Manufacturing	Kumar Janoria	Pei-I Chu
Microbiology	Avital Shimanovich	Julie Nemecek
Biopharmaceutics	Akm Khairuzzaman	Elsbeth Chikhale
Environmental	Raanan Bloom	Scott Furness
Regulatory Business Process Manager	Shamika Brooks	
Application Technical Lead	David Claffey	

U.S. FOOD & DRUG ADMINISTRATION

EXECUTIVE SUMMARY

I. RECOMMENDATIONS AND CONCLUSION ON APPROVABILITY

Recommend a Complete Response action from a product quality perspective based on the recommendation of the OPQ process and facilities review team due to the inadequate responses regarding (b) (4) *in the cabotegravir drug product and resulting withhold recommendation from a compliance perspective for the cabotegravir drug product manufacturing site (Glaxo, Barnard Castle, UK). Further, DMF* (b) (4) *for the rilpivirine drug product was found to be inadequate to support this application.*

Note that each of the other OPQ review teams found the application acceptable from their perspectives.

Deficiencies for CR Letter:

1.During a recent inspection of the GLAXO OPERATIONS UK LIMITED (FEI: 3002807078) manufacturing facility for this application, our field investigator conveyed deficiencies to the representative of the facility. Satisfactory resolution of these deficiencies is required before this application may be approved. Note that as a follow-up to the pre-approval inspection, a Post-Action Memorandum with outstanding concerns will be sent to the inspected drug product facility. Ensure that a future resubmission includes updates to the relevant modules of application in response to these deficiencies.

(b) (4)

(b) (4)

2.DMF (b) (4) *was found to be inadequate to support this application. The deficiencies communicated with the DMF holder will need to be resolved before this application can be approved.*

Additional request:
The proposed upper limit for the median drug product particle size acceptance range is significantly higher than that of that of pivotal clinical batches. We request that you tighten and further justify this limit.

II. SUMMARY OF QUALITY ASSESSMENTS

A. Product Overview

The proposed product is a kit containing two separate vialed extended release injectable products – one contains cabotegravir, a new molecular entity. The second vial contains the rilpivirine free base. Cabotegravir is an integrase inhibitor with a chemical structure similar to dolutegravir. Rilpivirine is an HIV-1 non-nucleoside reverse transcriptase inhibitor and is currently marketed as in its HCl salt form in oral dosage forms. Both products are suspensions of the drug substance in (b) (4) of excipients. Each product will be administered (via IM) monthly. The product's extended release characteristics (b) (4) The applicant proposes marketing two dosage strengths of the kits – designed to administer either 2 ml or 3 ml of each product. Both products are white suspensions. The suspension is drawn up from the vial with the co-packaged needle and syringe and administered within 120 minutes by gluteal injection. Each vial contains an overfill which requires the HCP to adjust the volume to either 2 ml or 3 ml before administration.

Cabotegravir extended release injectable suspension is a white to light pink, suspension containing 200 mg/mL of cabotegravir free acid. Each sterile, single-dose vial provides a dose of 400 mg/2 mL or 600 mg/3 mL for intramuscular (IM) administration. The product is supplied in a brown glass vial with a rubber injection stopper and sealed with an aluminum overseal with a removeable plastic cap in two nominal fill presentations, 2-mL and 3-mL. There is sufficient overfill in the vial for the user to withdraw just over the nominal fill volume. The volume of the syringe contents is adjusted to the nominal volume (2 ml or 3 ml) before administration.

One single-dose vial of Cabotegravir Injectable Suspension, 200 mg/mL is co-packaged with one single-dose vial of Rilpivirine 300 mg/mL extended-release injectable suspension, which is the subject of the cross referenced DMF (b) (4). Its characteristics are similar to the cabotegravir product, except that it is packaged in a clear, rather than brown, glass vial. Two dosage strengths will also be marketed - 600 mg/2 mL and 900 mg/3 mL.

The combination product co-packs contain:
400mg/600mg Kit:

- single-dose vial of 400 mg/2 ml of cabotegravir, 200 mg/mL
- single-dose vial of 600 mg/ 2ml of rilpivirine, 300 mg/mL

600 mg/900 mg Kit:

- single-dose vial of 600 mg/3ml of cabotegravir, 200 mg/mL
- single-dose vial of 900 mg/3ml of rilpivirine, 300 mg/mL

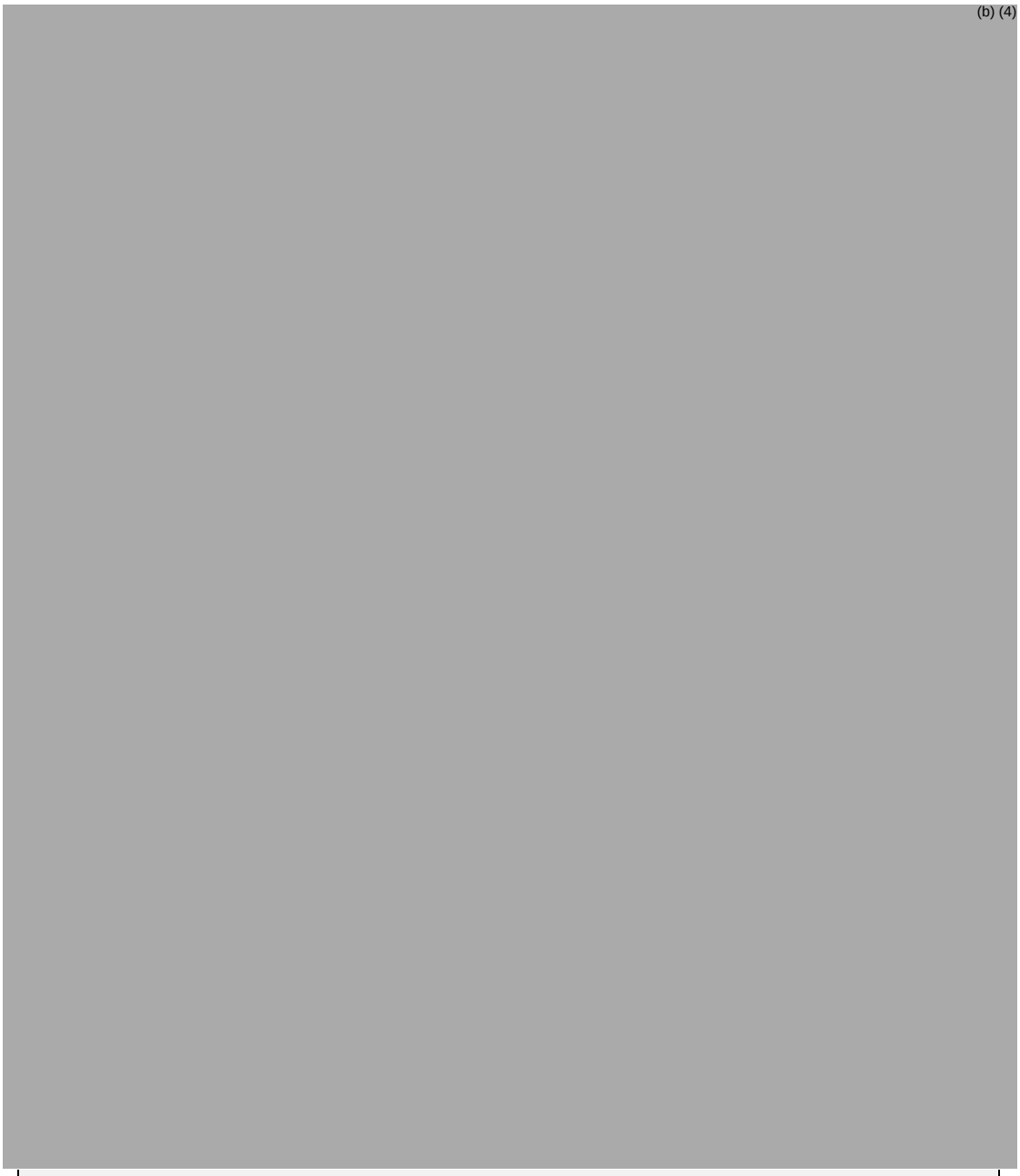
Drug products for each of the two fill presentations are co-packaged with the following aspiration and dosing devices:
2-mL co-pack and 3-mL co-pack

- two sterile, single-use vial adaptors
- two 5-mL sterile, single-use syringes
- two sterile, single-use 23 gauge, 1.5-inch safety needles

The drug products are intended to be dosed concomitantly as separate gluteal injections. No dilution is required prior to administration for either drug product.

Background to CR recommendation:
The CR recommendation from a process and facilities perspective is based on findings during and after the preapproval inspection of the cabotegravir drug

(b) (4)



Proposed Indication(s) including Intended Patient Population	Treatment of HIV 1
Duration of Treatment	Chronic
Maximum Daily Dose	
Alternative Methods of Administration	None.

B. Quality Assessment Overview

Drug Substance: Adequate

Cabotegravir: Cabotegravir is a new molecular entity. CMC information supporting cabotegravir drug substance was submitted to NDA 212888. Cabotegravir is practically insoluble in water but more soluble in many organic solvents. It contains two chiral centers. Several polymorphs are known but two are relevant to the proposed manufacturing process. (b) (4) The source of the potential impurities is adequately understood and demonstrated in several drug substance batches. The four specified impurities are controlled to (b) (4)% and other impurities to (b) (4)%. in accordance with (b) (4) qualification threshold and potential genotoxin control concurred with (b) (4) criteria.

Cabotegravir is manufactured in a (b) (4). The batch analyses data of 17 batches were provided, including the commercial validation, primary stability, clinical, and toxicological batches. All results met specification. Stability data on the three primary stability batches supports a retest period of (b) (4) months.

Rilpivirine: All CMC information supporting rilpivirine drug substance was referenced to DMF (b) (4). The DMF (b) (4) was found adequate to support this application. The information on drug substance characterization, manufacturing, control of all impurities including mutagenic, control (b) (4) batch analyses, and was found adequate Batch analyses data for 33 batches met specification. The proposed rilpivirine drug substance specification was adequately justified. The proposed (b) (4) month retest period was supported by (b) (4) Refer to the adequate DMF (b) (4) for additional details.

Drug Product: Adequate

NDA 212888 contained only information supporting cabotegravir extended release injectable suspension, one of the two products co-packaged in the to-be-marketed co-packaged product. The rilpivirine drug product is referenced to DMF (b) (4) (found to be adequate by the drug product review team). Marketing of two dosage strengths of cabotegravir product is proposed, 400 mg/2 mL and 600 mg/3 mL. The product is a white to light pink, suspension packaged in a brown glass vial with a rubber injection stopper and sealed with an aluminum overseal with a removeable plastic cap.

(b) (4)

The cabotegravir drug product vial contains an overfill of (b) (4) mL and (b) (4) mL for the 2-mL and 3-mL fill presentations, respectively. The cabotegravir drug product vial contains a suspension of drug substance in a solution of mannitol (b) (4), polysorbate 20 (b) (4) and PEG 335 (b) (4). The drug substance (b) (4)

The rilpivirine drug product contains drug substance suspended in (b) (4)

(b) (4)

hydroxide as pH adjuster. Its supporting information was provided in the referenced DMF (b) (4). It was found acceptable to support this NDA from a drug product review perspective.

The applicant's claim of categorical exclusion (21 CFR 25.31(b)) and provided statement of 'no extraordinary circumstance' was found acceptable by the environmental assessment team.

Labeling: Adequate

Labeling review includes several recommendations for changes to the PI and carton/container labeling.

Manufacturing: Inadequate

(b) (4)

(b) (4)

The proposed commercial batch size is the same as registration batch scale. The overall yields of the registration batches were found acceptable. Full details of the rilpivirine drug product manufacturing process was referenced to DMF (b) (4) which was found to be inadequate to support this application. The final kit containing the two drug products, two syringes, two needles and two vial adapters is assembled at the Glaxo UK site. All the related sites were found acceptable to support this application with the exception of the Glaxo site in Barnard Castle, UK (FEI: 3002807078). See above for background.

Biopharmaceutics: Adequate

The biopharmaceutics review team found the proposed drug release method for the cabotegravir drug product acceptable as a quality control test (Apparatus II, 20rpm; 1000mL of 0.5% w/v CTAB in 140 mM McIlvaine Buffer, pH 7.4, 37°C. Q= (b) (4)% at 45 min). The single point acceptance criterion was found acceptable, (b) (4) . The applicant provided adequate justification to bridge the pivotal clinical to the commercial product. The extended release claim was found acceptable.
The rilpivirine drug product's drug release method, bridging and extended release claim were also found acceptable (refer to DMF (b) (4).

Microbiology (if applicable): Adequate

The Cabotegravir drug product is (b) (4) The manufacturing process for the Rilpivirine drug product is described in DMF (b) (4); the (b) (4) Rilpivirine drug substance is described in DMF (b) (4). The information in the NDA and reference DMFs were found to adequately support product quality from a microbiology perspective. Note that although the cabotegravir (b) (4) .

D. List of Deficiencies for Complete Response

1.During a recent inspection of the GLAXO OPERATIONS UK LIMITED (FEI: 3002807078) manufacturing facility for this application, our field investigator conveyed deficiencies to the representative of the facility. Satisfactory resolution of these deficiencies is required before this application may be approved. Note that as a follow-up to the pre-approval inspection, a Post-Action Memorandum with outstanding concerns will be sent to the inspected drug product facility. Ensure that a future resubmission includes updates to the relevant modules of application in response to these deficiencies.

2.DMF (b) (4) *was found to be inadequate to support this application. The deficiencies communicated with the DMF holder will need to be resolved before this application can be approved.*

Additional request:

The proposed upper limit for the median drug product particle size acceptance range is significantly higher than that of that of pivotal clinical batches. We request that you tighten and further justify this limit.

Application Technical Lead Name and Date:

David Claffey, PhD, 26 NOV 2019

David Claffey

Digitally signed by David Claffey
Date: 11/26/2019 12:23:38PM
GUID: 508da71e00029e20b201195abff380c2

U.S. FOOD & DRUG ADMINISTRATION

QUALITY ASSESSMENT DATA SHEET

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Assessment Completed	Comments
(b) (4)	II	(b) (4)	(b) (4)	Inadequate	Nov 2019	Found adequate in separate reviews by (b) (4) review teams. Found inadequate by process and facilities
(b) (4)	II		(b) (4)	Adequate	OCT 2019	Found adequate in separate reviews by (b) (4) teams
(b) (4)	III	(b) (4)	(b) (4)	Adequate		
(b) (4)	III	(b) (4)	(b) (4)	Adequate		

2. CONSULTS

none

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CHAPTER IV: LABELING

IQA NDA Assessment Guide Reference

1.0 PRESCRIBING INFORMATION

Assessment of Product Quality Related Aspects of the Prescribing Information:

1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION

Item	Information Provided in the NDA	Assessor's Comments
Product Title in Highlights		
Proprietary name	CABENUVA	Adequate.
Established name(s)	cabotegravir extended-release injectable suspension; rilpivirine extended-release injectable suspension), co-packaged for intramuscular use	Adequate.
Route(s) of administration	Intramuscular	Adequate.
Dosage Forms and Strengths Heading in Highlights		
Summary of the dosage form(s) and strength(s) in metric system.	Cabotegravir extended-release injectable suspension and rilpivirine extended-release injectable suspension, co-packaged as follows: (3) CABENUVA 400-mg/600-mg Dosing Kit: • single-dose vial of 400 mg/2 mL (200 mg/mL) cabotegravir • single-dose vial of 600 mg/2 mL (300 mg/mL) rilpivirine CABENUVA 600-mg/900-mg Dosing Kit: • single-dose vial of 600 mg/3 mL (200 mg/mL) cabotegravir • single-dose vial of 900 mg/3 mL (300 mg/mL) rilpivirine	Adequate.
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	

For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	Single-dose	Adequate.

1.2 FULL PRESCRIBING INFORMATION

1.2.1 Section 2 (DOSAGE AND ADMINISTRATION)

Item	Information Provided in the NDA	Assessor's Comments
DOSAGE AND ADMINISTRATION section		
Special instructions for product preparation (e.g., reconstitution and resulting concentration, dilution, compatible diluents, storage conditions needed to maintain the stability of the reconstituted or diluted product)	Refer to the Instructions for Use for complete administration instructions with illustrations. A complete dose requires 2 injections: one injection of cabotegravir and one injection of rilpivirine [see Dosage and Administration (2.3)]. Cabotegravir and rilpivirine are suspensions for gluteal intramuscular injection that do not need further dilution or reconstitution. Before preparing the injections, remove CABENUVA from the refrigerator and wait at least 15 minutes to allow the medicines to come to room temperature. The vials may remain in the carton at room temperature for up to 6 hours. If not used after 6 hours, the medication must be discarded. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. The cabotegravir vial has a brown tint to the glass which may limit visual inspection. Discard CABENUVA if either medicine exhibits particulate matter or discoloration. Shake each vial of CABENUVA vigorously so that the suspensions look uniform before injecting. Small air bubbles are expected and acceptable. Once the suspensions have been drawn into the respective syringes, the injections should be administered as soon as possible, but may remain in the syringes for up to 2 hours. If 2 hours are exceeded, the medication, syringes, and needles must be discarded [see How Supplied/Storage and Handling (16)].	Adequate. The in-use conditions are supported by in-use stability results.

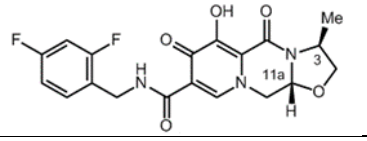
1.2.2 Section 3 (DOSAGE FORMS AND STRENGTHS)

Item	Information Provided in the NDA	Assessor's Comments
DOSAGE FORMS AND STRENGTHS section		
Available dosage form(s)	CABENUVA contains a single-dose vial of cabotegravir as a white to light pink, free-flowing extended-release injectable suspension and a single-dose vial of rilpivirine as a white to off-white extended-release injectable suspension, co-packaged as follows: CABENUVA 400-mg/600-mg Kit • Injection: 400 mg/2 mL (200 mg/mL) of cabotegravir suspension in single-dose vial • Injection: 600 mg/2 mL (300 mg/mL) of rilpivirine suspension in single-dose vial CABENUVA 600-mg/900-mg Kit • Injection: 600 mg/3 mL (200 mg/mL) of cabotegravir suspension in single-dose vial • Injection: 900 mg/3 mL (300 mg/mL) of rilpivirine suspension in single-dose vial	Adequate.
Strength(s) in metric system	See above.	Adequate.
If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance	N/A	
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting	See above.	Adequate.
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	

For injectable drug products for parental administration, use appropriate labeling term (e.g., single-dose, multiple-dose, single-patient-use). Other package type terms include pharmacy bulk package and imaging bulk package.	Single-dose	Adequate.

1.2.3 Section 11 (DESCRIPTION)

Item	Information Provided in the NDA	Assessor's Comments
DESCRIPTION section		
Proprietary and established name(s)	CABENUVA, cabotegravir extended-release injectable suspension; rilpivirine extended-release injectable suspension), co-packaged for intramuscular use	Adequate.
Dosage form(s) and route(s) of administration	Injectable suspension for intramuscular injection	Adequate.
If the active ingredient is a salt, apply the USP Salt Policy and include the equivalency statement per FDA Guidance.	N/A	
List names of all inactive ingredients. Use USP/NF names. Avoid Brand names.	citric acid monohydrate (1 mg/mL); poloxamer 338 (50 mg/mL); Water for Injection; glucose monohydrate to ensure isotonicity; and sodium dihydrogen phosphate monohydrate and sodium hydroxide to adjust pH	Adequate.
For parenteral injectable dosage forms, include the name and quantities of all inactive ingredients. For ingredients added to adjust the pH or make isotonic, include the name and statement of effect.	See above	Adequate.
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	N/A	
Statement of being sterile (if applicable)	Yes	Adequate.
Pharmacological/ therapeutic class	Cabotegravir: HIV INSTI Rilpivirine: HIV NNRTI	Adequate.

Chemical name, structural formula, molecular weight	Cabotegravir: The chemical name for cabotegravir is (*3S,11aR*)-N-[(2,4-difluorophenyl)methyl]-6-hydroxy-3-methyl-5,7-dioxo-2,3,5,7,11,11a-hexahydro[1,3]oxazolo[3,2-a]pyrido[1,2-d]pyrazine-8-carboxamide.The empirical formula is $C_{19}H_{17}F_2N_3O_5$ and the molecular weight is 405.35 g/mol. It has the following structural formula: 	Adequate.
If radioactive, statement of important nuclear characteristics.	N/A	
Other important chemical or physical properties (such as pKa or pH)	N/A	

Section 11 (DESCRIPTION) Continued

Item	Information Provided in the NDA	Assessor's Comments
For oral prescription drug products, include gluten statement if applicable	N/A	
Remove statements that may be misleading or promotional (e.g., "synthesized and developed by Drug Company X," "structurally unique molecular entity"	N/A	

1.2.4 Section 16 (HOW SUPPLIED/STORAGE AND HANDLING)

Item	Information Provided in the NDA	Assessor's Comments
HOW SUPPLIED/STORAGE AND HANDLING section		
Available dosage form(s)	CABENUVA is supplied in 2 dosing kits. Each kit contains one vial of cabotegravir extended-release injectable suspension and rilpivirine extended-release injectable suspension, co packaged as follows: CABENUVA 400-mg/600-mg Kit (NDC 49702-253-15) containing: • One single-dose vial of cabotegravir extended-release injectable suspension containing 400 mg/2 mL (200 mg/mL) of cabotegravir. • One single-dose vial of rilpivirine extended-release injectable suspension containing 600 mg/2 mL (300 mg/mL) of rilpivirine CABENUVA 600-mg/900-mg Kit (NDC 49702-240-15) containing: • One single-dose vial of cabotegravir extended-release injectable suspension containing 600 mg/3 mL (200 mg/mL) of cabotegravir. • One single-dose vial of rilpivirine extended-release injectable suspension containing 900 mg/3 mL (200 mg/mL) of rilpivirine.	Adequate.
Strength(s) in metric system	Yes; see above.	Adequate.
Available units (e.g., bottles of 100 tablets)	(b) (4)	Adequate.
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	Yes; see above.	Adequate.

Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state “functionally scored”	N/A	
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	Single-dose	Adequate.

Section 16 (HOW SUPPLIED/STORAGE AND HANDLING) (Continued)

Item	Information Provided in the NDA	Assessor’s Comments

Special handling about the supplied product (e.g., protect from light, refrigerate). If there is a statement to “Dispense in original container,” provide reason why (e.g. to protect from light or moisture, to maintain stability, etc.)	Store CABENUVA in the refrigerator at 2°C to 8°C (36°F to 46°F) in the original carton until ready to use. Do not freeze. Do not mix with any other product or diluent. Prior to administration, vials should be brought to room temperature (not to exceed 25°C [77°F]). Vials may remain in the carton at room temperature for up to 6 hours. If not used after 6 hours, they must be discarded. Once the suspension has been drawn into the respective syringes, the injections should be administered as soon as possible, but may remain in the syringe for up to 2 hours. If 2 hours are exceeded, the medications, syringes, and needles must be discarded.	Adequate. The shelf life and in-use conditions are supported by stability results.
If the product contains a desiccant, ensure the size and shape differ from the dosage form and desiccant has a warning such as “Do not eat.”	N/A	
Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature.	2°C to 8°C (36°F to 46°F)	Adequate.
Latex: If product does not contain latex and manufacturing of product and container did not include use of natural rubber latex or synthetic derivatives of natural rubber latex, state: “Not made with natural rubber latex. Avoid statements such as “latex-free.”	The vial stoppers and vial adapters are not made with natural rubber latex.	Adequate.

Include information about child-resistant packaging	N/A	

1.2.5 Other Sections of Labeling
N/A

1.2.6 Manufacturing Information After Section 17 (for drug products)

Item	Information Provided in the NDA	Assessor's Comments
Manufacturing Information After Section 17		
Name and location of business (street address, city, state and zip code) of the manufacturer, distributor, and/or packer	GlaxoSmithKline Research Triangle Park, NC 27709	Adequate.

2.0 PATIENT LABELING

Assessment of Product Quality Related Aspects of Patient Labeling (e.g., Medication Guide, Patient Information, Instructions for Use):
The product is to be administered by healthcare professionals only. The IFU was reviewed by DMEPA.

3.0 CARTON AND CONTAINER LABELING

3.1 Container Label
See section 1.14

3.2 Carton Labeling
See section 1.14

Item	Information Provided in the NDA	Assessor's Comments about Carton Labeling
Proprietary name, established name, and dosage form (font size and prominence)	CABENUVA, cabotegravir extended-release injectable suspension, 400 mg/2 mL (200 mg/mL) co-packaged with rilpivirine extended-release injectable suspension, 600 mg/2 mL (300 mg/mL)	Adequate. The language on the left is for the 400 mg/600 mg Kit. The language for 600 mg/900 mg Kit is identical with the exception of the dose strengths.
Dosage strength	400-mg/600-mg Kit (NDC 49702-253-15): Cabotegravir - 400 mg/2 mL (200 mg/mL); Rilpivirine – 600 mg/2 mL (300 mg/mL) 600-mg/900-mg Kit (NDC 49702-240-15) Cabotegravir - 400 mg/2 mL (200 mg/mL); Rilpivirine – 600 mg/2 mL (300 mg/mL)	Adequate.
Route of administration	For gluteal intramuscular use only.	Adequate.
If the active ingredient is a salt, include the equivalency statement per FDA Guidance	N/A	
Net contents (e.g. tablet count)	-1 cabotegravir single-dose vial -1 rilpivirine single-dose vial -2 vial adapters -2 syringes -2 injection needles (23 gauge, 1½ inch) -2 syringe labels -Prescribing information -Patient information -Instructions for use	Adequate.
"Rx only" displayed on the principal display	Yes	Adequate.
NDC number	Yes, see above	Adequate.
Lot number and expiration date	Yes	Adequate.

Storage conditions. If applicable, include a space on the carton labeling for the user to write the new BUD.	Store in refrigerator at 2°C to 8°C (36°F to 46°F). Do not freeze. Discard unused portion.	Adequate.
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use)	Single-dose vial	Adequate.
Other package terms include pharmacy bulk package and imaging bulk package which require “Not for direct infusion” statement.	N/A	
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	N/A	
Bar code	Yes	Adequate.

Item	Information Provided in the NDA	Assessor's Comments about Carton Labeling
Name of manufacturer/distributor	Manufactured for: Viiv Healthcare Research Triangle Park, NC 27709 By: GlaxoSmithKline Research Triangle Park, NC 27709 (b) (4)	Adequate.
Medication Guide (if applicable)	N/A	
No text on Ferrule and Cap overseal	Yes	Adequate.
When a drug product differs from the relevant USP standard of strength, quality, or purity, as determined by the application of the tests, procedures, and acceptance criteria set forth in the relevant compendium, its difference shall be plainly stated on its label.	N/A	
And others, if space is available	N/A	

Assessment of Carton and Container Labeling: Adequate.

ITEMS FOR ADDITIONAL ASSESSMENT

N/A

Overall Assessment and Recommendation:

Based on this labeling review, the sections herein are adequate for approval.

Primary Labeling Assessor Name and Date:

Pete Guerrieri, PhD, Branch 3; Division of New Drug Product I.

Secondary Assessor Name and Date (and Secondary Summary, as needed):

Peter Guerrieri

Digitally signed by Peter Guerrieri
Date: 11/09/2019 11:36:30AM
GUID: 54eb8ba100062ea99cbaab7c64143df3

Balajee Shanmugam

Digitally signed by Balajee Shanmugam
Date: 11/09/2019 06:05:44PM
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CHAPTER VII: MICROBIOLOGY

IQA NDA Assessment Guide Reference

Product Information	
NDA Number	212888
Assessment Cycle Number	01
Drug Product Name/ Strength	CABENUVA, co-pack of cabotegravir 200 mg/mL and rilpivirine 300 mg/mL
Route of Administration	Intramuscular injection
Applicant Name	ViiV Healthcare Company
Therapeutic Classification/ OND Division	Division of Antiviral Products
Manufacturing Site	Cabotegravir: Glaxo Operations UK Limited (trading as Glaxo Wellcome Operations) Harmire Road Barnard Castle County Durham DL128DT UK Rilpivirine: (b) (4)
Method of Sterilization	Cabotegravir: (b) (4) Rilpivirine: (b) (4)

Assessment Recommendation: **Adequate**

Assessment Summary:

Document(s) Assessed	Date Received
Original submission Multiple Categories/CMC and Microbiology IR responses	04/29/2019 07/05/2019, 08/19/2019, 09/25/2019, 10/15/2019, 10/21/2019

List Submissions being assessed: See table above

Highlight Key Issues from Last Cycle and Their Resolution: N/A

Remarks: The drug products are packaged in a kit with components. The components are purchased as sterile. The Cabotegravir drug product is (b) (4) The manufacturing process for the Rilpivirine drug product is described in DMF (b) (4); the (b) (4) Rilpivirine drug substance is described in DMF (b) (4).

Concise Description of Outstanding Issues: None

Supporting Documents:

- DMF (b) (4) for the (b) (4) Rilpivirine drug substance (Subject: Rilpivirine Drug Substance, Holder: (b) (4)
- Microbiology review (b) (4).docx for the Rilpivirine drug substance, dated 09/10/2019 (V-drive), and found adequate.
- DMF (b) (4) for the Rilpivirine drug product (Subject: Rilpivirine extended release suspension for injection, Holder: (b) (4) .
- Microbiology review (b) (4).docx, dated 09/10/2019 (V-drive), for the Rilpivirine drug product.

S DRUG SUBSTANCE

The Cabotegravir drug substance is (b) (4), and the drug product is subject to (b) (4)

The Rilpivirine drug substance is (b) (4) The applicant references Type II DMF (b) (4) for the manufacture and (b) (4) of the drug substance. An LoA is provided in Section 1.4.2 from (b) (4) dated 04/24/2019 to reference the DMF for information regarding the Rilpivirine drug substance.

Assessment: ***Adequate***

The Cabotegravir drug substance will not be assessed for microbiological quality.

The Rilpivirine drug substance is reviewed for (b) (4) in microbiology review (b) (4).docx (V-drive), dated 08/07/2019, and found adequate.

P.1 DESCRIPTION OF THE COMPOSITION OF THE DRUG PRODUCT

Section 3.2.P.1, "Description and Composition of the Drug Product"

The drug products are co-packaged in the following 2 configurations:

2 mL co-pack	**3 mL co-pack**
Cabotegravir, 2 mL fill	Cabotegravir, 3 mL fill
Rilpivirine, 2 mL fill	Rilpivirine, 3 mL fill
2 sterile, single-use vial adaptors	
2 5-mL sterile, single-use syringes	

2 sterile, single-use 23G 1.5-inch safety needles

Assessment: ***Adequate***

The NDA includes two co-packaged (b) (4) drug products, Cabotegravir and Rilpivirine, and components. Therefore, the microbiological assessment of the drug products will consist of three sections: an assessment of the components, followed by an assessment of the Cabotegravir drug product, followed by an assessment of the Rilpivirine drug product.

Microbiological Quality Assessment of the Co-packaged Components

The drug products are co-packaged with two sterile single-use adaptors, two 5-mL sterile single-use syringes, and two sterile single use 23G 1.5 inch safety needles. The sterilization of the components was not described.

Information request:

The following IR was sent to the applicant on 08/02/2019.

We acknowledge that the Cabotegravir and Rilpivirine drug products are co-packaged with two sterile single-use adaptors, two 5-mL sterile single-use syringes, and two sterile single-use 23G 1.5 inch safety needles. However, the sterilization information for the co-packaged components could not be located. Therefore, clarify if these components are purchased as sterile or sterilized in-house. If any of the components are purchased as sterile, provide the 510(k) numbers. If any of the components are sterilized in-house, then provide a complete description of the sterilization method, parameters, and validation studies including results from three runs with at least one run performed recently (within the past 1-2 years).

Information request response:

The following IR response was received on 08/19/2019.

The applicant states that all of the components are purchased as sterile, and the 510(k) references were provided in section 3.2.R_Attachment_Devices of the original submission. The applicant also provided the 510(k) numbers in the IR response which are provided below:

Component	Supplier	510(k) #
two sterile single-use adaptors	(b) (4)	
two 5-mL sterile single-use syringes		
two sterile single-use 23G 1.5 inch safety needles		

Assessment: ***Adequate***

The applicant provided the 510(k) numbers for the sterile components.

Microbiological Quality Assessment of the Cabotegravir Drug Product

- **Description of the drug product** – Cabotegravir is a single-use, white to light pink, sterile solution.

- **Drug Product composition** – The Cabotegravir drug product composition is as follows:

Ingredient	Quantity per 2 mL dose	Quantity per 3 mL dose	Function
Cabotegravir	400 mg	600 mg	API
Mannitol	70 mg	105 mg	(b) (4)
Polysorbate 20	40 mg	60 mg	
Polyethylene glycol 3350	40 mg	60 mg	
Water for injection (WFI)	q.s.	q.s.	

- **Description of container closure system –** The Cabotegravir drug product container closure system (CCS) is as follows:

Component	Fill Volume	Description	Source
Vial	2 mL	(b) (4) mL/13 mm Type (b) (4) glass vial (brown (b) (4)	(b) (4)
	3 mL	(b) (4) mL/13 mm Type (b) (4) glass vial (brown (b) (4)	
Stopper	2 mL	13 mm rubber grey (b) (4) stopper	
	3 mL		
Seal	2 mL	13 mm aluminum dark grey cap	
	3 mL	13 mm aluminum orange cap	

Assessment: ***Adequate***

The applicant provided a description of the Cabotegravir drug product and CCS.

P.2 PHARMACEUTICAL DEVELOPMENT
P.2.5 MICROBIOLOGICAL ATTRIBUTES

(b) (4)

Avital Shimanovich

Digitally signed by Avital Shimanovich
Date: 10/25/2019 11:24:51AM
GUID: 598ca8f5005723e97e9300810ca9b31a

Julie Nemecek

Digitally signed by Julie Nemecek
Date: 10/28/2019 06:50:31AM
GUID: 5277e82100088e39e79f3393e72134cf

CHAPTER III: ENVIRONMENTAL

IQA NDA Assessment Guide Reference

R REGIONAL INFORMATION

Environmental Analysis

Application: NDA 212888

Drug product: CABENUVA (cabotegravir extended-release injectable suspension; rilpivirine extended-release injectable suspension), co-packaged for intramuscular use.

Indication: Indicated as a complete regimen for the treatment of HIV-1 infection in adults to replace the current antiretroviral regimen in those who are virologically suppressed (HIV-1 RNA less than 50 copies per mL) and who have no known or suspected resistance to either cabotegravir or rilpivirine.

Proposed doses: 300mg/1mL || 200mg/1mL

Mechanism of action: CABENUVA contains 2 long-acting HIV-1 antiretroviral agents, cabotegravir and rilpivirine

Claim of Categorical Exclusion: The applicant has submitted a claim of categorical exclusion under 21 CFR 25.31(b) and a statement of 'no extraordinary circumstances' under 21 CFR 25.21. Sales production volumes for rilpivirinre and expected environmental concentration are provided by the applicant. Environmental effects studies were submitted by the applicant.

***Note**: NDA 212888 (CABENUVA) is a combination product of cabotegravir and rilpivirine. Cabotegravir was reviewed under NDA 212887; the submitted claim of categorical exclusion was found acceptable. This review considers the environmental impact of rilpivirine alone. Modeling analysis was conducted and the applicant provided additional information in response to an IR.*

Reviewer's Assessment: Adequate

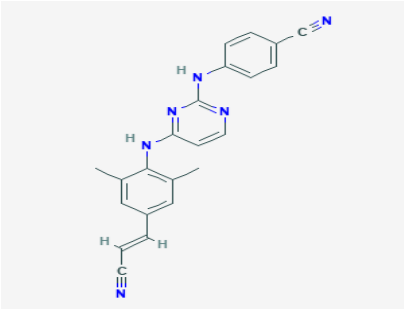
The applicant's claim of categorical exclusion (21 CFR 25.31(b)) and provided statement of 'no extraordinary circumstance' are acceptable.

- Modeled acute and chronic toxicity values show safety margins between exposure concentrations and effects.
- An EMA ecotoxicity risk assessment for rilpivirine showed the EIC (b) (4) µg/L) to be approx. (b) (4)-fold lower than the NOEC for the most sensitive organisms in a Early Life Stage zebrafish (*Danio rerio*) Toxicity Test.
- The Fish Plasma Model output indicates that additional chronic studies may be required for NDA supplements that increase use significantly.

- Some studies with rilpivirine indicate a potential endocrine disruption in mammalian systems. To address this, the applicant argues that the effects noted for thyroid, testes and ovaria should be considered secondary or related to a rodent specific mechanism.
- Based on the expected low environmental concentrations of rilpivirine in surface waters (EIC = (b) (4) µg/L; EEC = (b) (4) µg/L), and favorable exposure/effects ratios, significant environmental impacts are not anticipated due to approval of this application. Additional chronic and reproduction/developmental studies with aquatic organisms may be required for NDA supplements that increase use significantly.

Application Review

API: RILPIVIRINE
CASRN: 500287-72-9
MW: 366.43 g/mol



- The applicant provides a 5 production estimate for all formulations of rilpivirinre of approximately (b) (4) kg of drug substance per year. This results in an EIC of < (b) (4) µg/L. The EEC = (b) (4) µg/L (NDA Categorical Exclusion for rilpivirine long acting/Doc. #: TMC278 - JNJ-16150108-AAA).
- Log Kow = (b) (4)
- BCF_{fish} = (b) (4)
- EC_{fish} = (b) (4) µg/L
- C_{max} (Human therapeutic concentration; month 3 onward following 400 mg monthly IM dose) = (b) (4) µg/L

Several models were used to estimate rilpivirinre toxicity and potential cellular activity

FISH PLASMA MODEL (Human therapeutic concentration)

Source	C_{max} (Human Therapeutic Conc) (µg/L)	EC_{fish} (µg/L)	Effect ratio
Module 2.4. Non-clinical overview	(b) (4)	(b) (4)	(b) (4)

Effect ratio = EC_{fish}/C_{max}

- Fish plasma model result of ER< (b) (4) indicate prioritization of fish chronic studies with rilpivirine may be needed.

MODEL PREDICTIONS

1. **Aquatic Toxicity predictions (Danish QSAR DB)**

- Data for top 4 analogues were retrieved. Two analogues have similarity index of (b) (4) and 2 analogues have similarity index of (b) (4).
- Fathead minnow: 96h LC_{50} estimated to range from (b) (4) to (b) (4) mg/L= (b) (4) µg/L
- *Daphnia magna*: 48h EC_{50} estimated to range from (b) (4) to (b) (4) mg/L= (b) (4) µg/L
- Pseudokirchneriella s.: 72h EC_{50} estimated to range from (b) (4) µg/L to (b) (4) mg/L
- Daphnia is predicted to be most sensitive organism based on analogue data.
- The lowest predicted acute toxicity value (b) (4) µg/L) is (b) (4)-fold higher than the EIC (b) (4) µg/L).

2. ECOSAR

- QSAR predictions for acute and chronic effects
- Functional groups: vinyl/allyl/propargyl nitrile

2.1 ACUTE TOXICITY

- Lowest predicted acute toxicity values for fish (LC50_96h): (b) (4) mg/L = (b) (4) µg/L
- Lowest predicted acute toxicity values for Daphnid (LC50_48h) (b) (4) mg/L = (b) (4) µg/L
- Lowest predicted acute toxicity values for green algae (EC50_96h): (b) (4) mg/L = (b) (4) µg/L
- Lowest predicted acute toxicity value for most sensitive organism (algae) is > (b) (4) fold higher than the EIC.

2.2 CHRONIC TOXICITY

- Lowest predicted chronic toxicity values for fish: (b) (4) mg/L = (b) (4) µg/L
- Lowest predicted chronic toxicity values for Daphnid: (b) (4) mg/L = (b) (4) µg/L
- Lowest predicted chronic toxicity values for green algae: (b) (4) mg/L = (b) (4) µg/L
- Lowest predicted chronic toxicity value for most sensitive organism (green algae) is (b) (4)-fold higher than the EIC.

3. QSARs for estrogen receptor (ER) and androgen receptor (AR) activity:

- Predictions for ER activity reported in Mansouri et al., 2016 (CERAPP): INACTIVE in ER binding, agonist, and antagonist consensus models.
- AR models: INACTIVE in AR binding, agonist, and antagonist models (OCHEM models).

EMA Ecotoxicity risk assessment for rilpivirine

Source: https://www.ema.europa.eu/en/documents/assessment-report/edurant-epar-public-assessment-report_en.pdf

Study type	Test protocol	Endpoint	Value	Unit	Remarks
Algae, Growth Inhibition	OECD 201	NOEC	≥ (b) (4)	µg/L	*Scenedesmus subspicatus*
Daphnia sp. Reproduction Test	OECD 211	NOEC	≥	µg/L	
Fish, Early Life Stage Toxicity Test/Species	OECD 210	NOEC	≥	µg/L	*Danio rerio*

Activated Sludge, Respiration Inhibition	OECD 209	NOEC	≥ (b) (4)	mg/L	

- EIC (b) (4) µg/L) is ~ (b) (4) **-fold lower** than the NOEC for most sensitive organism (fish).

Information Request (IR)

IR (Question 12), received by the applicant 29 July 2019, requested the applicant to provide additional information to support the submitted claim of categorical exclusion and provided statement of 'no extraordinary circumstances.' The applicant was referred to FDA's Guidance for Industry: Environmental Assessment: Questions and Answers Regarding Drugs with Estrogenic, Androgenic, or Thyroid Activity. Additional information should address the potential toxicity of rilpivirine to aquatic organisms at environmentally relevant concentrations.

RESPONSE to Q12 (CMC responses to questions received by applicant on 29 July 2019) was provided on August 9, 2019 (EDR: Application 212888 - Sequence 0019 - 0019 (21) 08/09/2019 ORIG-1 /Quality/Response To Information Request)

The applicant provided results of several aquatic toxicity studies and a risk characterization:

Table 2: Summary of the Results of the Microbial and Aquatic Effects:

Test title	Test guideline	Test duration	Endpoint (mg/L)
Algal growth inhibition (*Scenedesmus subspicatus*)	OECD 201	72 hours	Growth rate NOEC ≥ (b) (4) µg/L (mean measured conc.)
Daphnia reproduction (*Daphnia magna*)	OECD 211	21 days	21d-NOEC ≥ (b) (4) µg/L
Fish early life stage test *(Brachydanio rerio)*	OECD 210	35 days	NOEC ≥ (b) (4) µg/L
Activated sludge, respiration inhibition test[d]	OECD 209	3 hours	NOEC > (b) (4) mg/L

Environmental risk characterization is conducted by dividing the lowest EC_{50} (for acute testing) or NOEC (for chronic testing) by the EEC. The lowest NOEC from the three chronic toxicity studies (algae, *Daphnia magna* and fish) is the NOEC of (b) (4) µg/L for zebra fish. The EEC was calculated to be (b) (4) µg/L. This results in a risk characterization of (b) (4) (margin of safety> (b) (4).

With regards to rilpivirine as a potential endocrine disrupter, the applicant argues that "from a number of nonclinical studies with rilpivirine in dogs and rats, it can be concluded that rilpivirine should not be considered an endocrine disruptor, as there is no direct impact on cell receptors or circulating hormones, rather the effects noted thyroid, testes and ovaria are considered secondary or related to a rodent specific mechanism".

Primary Environmental Assessor Name and Date:

Secondary Assessor Name and Date (and Secondary Summary, as needed):

Raanan Bloom

Digitally signed by Raanan Bloom
Date: 10/28/2019 06:24:16PM
GUID: 508da72a0002a6d1071f3297897e4f1f

Michael Furness

Digitally signed by Michael Furness
Date: 10/29/2019 08:29:56AM
GUID: 502e8c7600003dd8331cf6eebf43697a

U.S. FOOD & DRUG ADMINISTRATION

CHAPTER VI: BIOPHARMACEUTICS

Product Information	CABOTEGRAVIR & RILPIVIRINE Extended Release Suspension for Intramuscular Injection (two separate co-packaged vials)
NDA Number	212888
Assessment Cycle Number	SDN 001
Drug Product Name/ Strength	CABENUVA (cabotegravir, rilpivirine) Extended-Release Injectable Suspension, 200 mg/ml and 300 mg/ml
Route of Administration	Intramuscular
Applicant Name	ViiV Healthcare Company
Therapeutic Classification/ OND Division	Antiviral Products
LD/RS Number	N/A
Proposed Indication	Treatment of HIV

Assessment Recommendation: **Adequate**

Assessment Summary: The proposed drug product is a co-packaged combination product submitted as a 505 (b)(1) NDA. One single-use vial of cabotegravir Injectable Suspension, 200 mg/mL is co-packaged with one single-use vial of rilpivirine 300 mg/mL Extended-release Suspension for Injection. Biopharmaceutics related information with respect to cabotegravir extended release injectable suspension is submitted in this NDA, and for rilpivirine extended release injectable suspension the information has been submitted to DMF-(b) (4). A letter of Authorization dated 04/23/2019 allowing FDA to reference DMF (b) (4) in support of NDA 212888 is provided. This Biopharmaceutics review was focused on the evaluation of the adequacy of the overall information/data for cabotegravir extended release injectable suspension supporting; **1)** the proposed drug release method and acceptance criteria, **2)** bridging of Phase III to commercial product, if needed, and **3)** evaluation of the extended release claim. Reference is made to the Biopharmaceutics review of DMF (b) (4) for the evaluation of the rilpivirine extended release injectable suspension. Based on the review of the provided information/data, Biopharmaceutics has the following conclusions:

1. DISSOLUTION/DRUG RELEASE TEST:

Drug Release Method and Acceptance Criteria: The Applicant's proposed drug release methods:

Cabotegravir extended release injectable suspension: [*USP apparatus II (Paddle) at 20±2 rpm; 1000±10 mL of 0.5% w/v solution of cetyltrimethylammonium bromide (CTAB) in 140 mM McIlvaine Buffer, pH 7.4 ±0.05 at 37℃, HPLC, sampling filter used 0.2 µ, sample amount/volume placed in each dissolution vessel: 250 µL of the suspension from each vial*] and acceptance criterion of Q=(b) (4)% at 45 min are **acceptable** for batch release and on stability.

Rilpivirine extended release injectable suspension**: See Biopharmaceutics review of DMF** (b) (4). DMF (b) (4) was found adequate from a Biopharmaceutics perspective to support NDA 212888.

2. EXTENDED RELEASE CLAIM: ***Acceptable.*** *The dosage form for both* cabotegravir and rilpivirine is extended release injectable suspension.

3. BRIDGING:

The Phase 3 cabotegravir extended release injectable suspension formulation composition and manufacturing site are identical to that of the commercial drug product. Therefore; bridging between different formulations and manufacturing sites is not needed. ***Acceptable***.

4. RISK ASSESSMENT: The table below shows the initial and final review assessment for the CQA-dissolution variable of cabotegravir extended release injectable suspension.

CQAs	Initial Risk Ranking	Comments	Updated Risk Ranking after Assessment Cycle #	Comments
Dissolution	Medium to high	(b) (4)	low	(b) (4)) are important and relevant for the proposed drug product.

List Submissions being assessed (table):

Document(s) Assessed	Date Received
SDN-001	04/29/2019
SDN-016	07/17/2019
SDN-019	08/09/2019

Highlight Key Issues from Last Cycle and Their Resolution: *None*

Concise Description of Outstanding Issues (List bullet points with key information and update as needed): *None*

B.1 BCS DESIGNATION

Solubility data:

Cabotegravir is practically insoluble below pH 9 and slightly soluble above pH 10 in aqueous media.

Table 1. Solubility of Cabotegravir.

Buffer, pH at 37°C	4 hours		24 hours	
	Solubility (mcg/mL)	Measured pH	Solubility (mcg/mL)	Measured pH
0.1N HCl, pH 1	6.8	1.0	6.7	1.0
Citric Ac/K_3PO_4, pH 2	9.0	2.2	9.3	2.2
Citric Ac/K_3PO_4, pH 3	8.3	3.0	7.9	3.0
Acetate, pH 4.5	8.0	4.6	2.7	4.6
Acetate, pH 5.5	7.0	5.7	4.3	5.7
Phosphate, pH 6.8	7.3	7.1	5.3	7.0
Phosphate, pH 7.4	8.8	7.7	6.8	7.6
Water	14.2	7.3	11.8	7.8

(b) (4)

[redacted]

Assessment: Acceptable

A BCS designation is not applicable since the proposed drug product is not an oral dosage form.

B.2 DISSOLUTION/DRUG RELEASE METHOD AND ACCEPTANCE CRITERIA

Method Development:

(b) (4)

[redacted]

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Drug Release Acceptance Criterion: The drug release acceptance criterion (Q (b) (4)% at 45 min) is acceptable based on the drug release data for the clinical batches and stability data. ***Acceptable***.

Reviewer's Final Evaluation: The proposed drug release method and acceptance criterion are acceptable for quality control.

B.3 EXTENDED RELEASE DOSAGE FORMS –*Extended Release Claim*

(b) (4)

Once both drug products are injected at separate gluteal injection sites, the drugs are slowly released from the administration site over the time period of a month. The elimination half-life of these drugs is 13 to 28 and 6 to 12 days for Rilpivirine and Cabotegravir, respectively. Both drug products do not show any dose dumping in vivo (refer to PK profiles under clinical module 5). For Cabotegravir and Rilpivirine, steady state is reached at approximately 44 weeks, consistent with the Phase 3 study. The results of the steady state plasma profile concentrations are shown below in Figure 9 and 10:

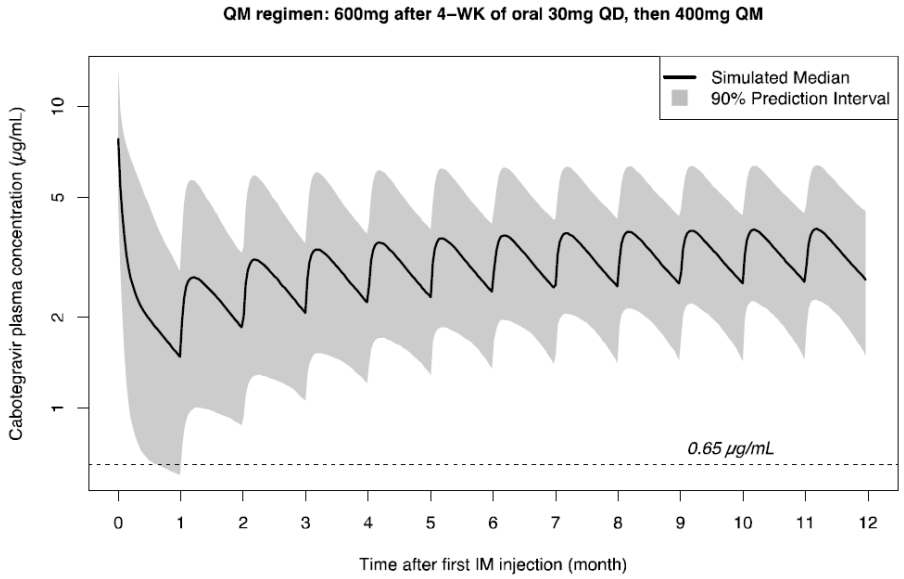

Fig. 9. Cabotegravir plasma steady state profile.

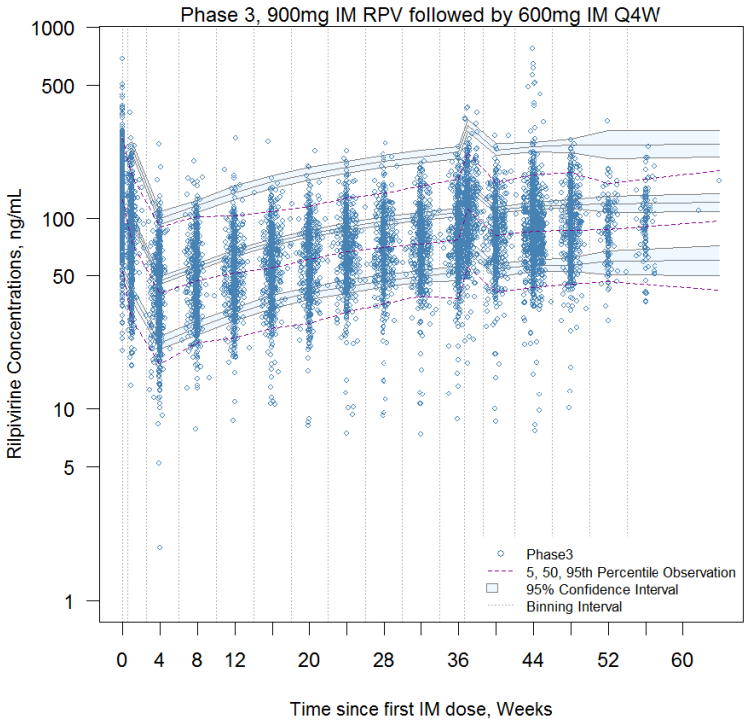

Fig. 10. Rilpivirine plasma profile from phase 3 study

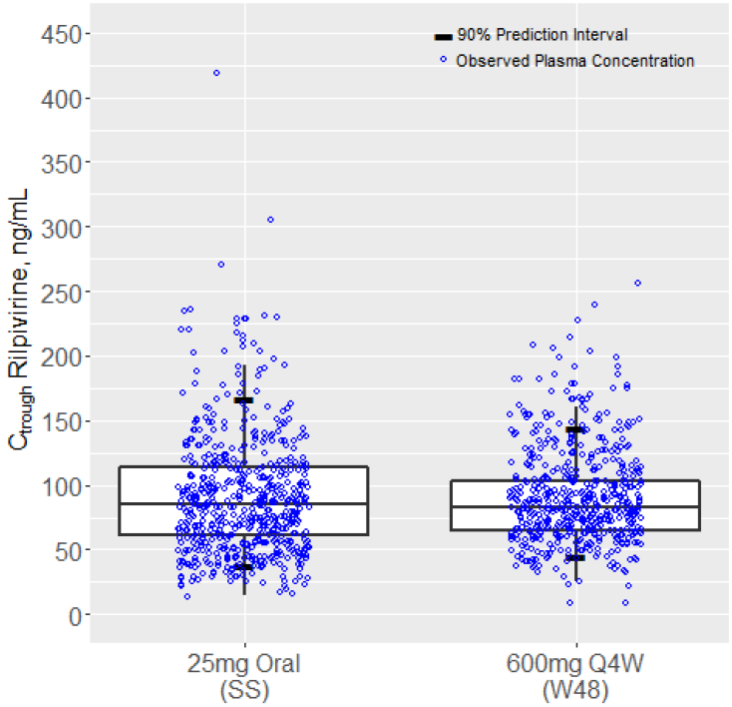

Fig. 11. Comparison of Observed and Simulated Distribution of C_{trough} After Oral and IM administration of Ripivirine

Prior to initiating treatment by intra muscular injection, both drugs are given orally (30 mg of Cabotegravir & 25 mg of Rilpivirine) once daily for 4 weeks, as IR tablets.

Assessment: *Adequate*
According to 21CFR 320.25 (f), both the drug products met the following criteria:

(i) Both drug products exhibit long plasma profile (over a month) and did not show any dose dumping.
(ii) The drug product's steady-state performance is equivalent to a currently marketed oral drug products (IR tablets).
(iii) The drug product's formulation provides consistent pharmacokinetic performance between individual dosage units.

B.4 BRIDGING OF FORMULATIONS

The following table summarizes all formulations used in clinical trials:

Component	**Quantity (mg/mL)**			
	Phase 1 formulation	Formulation A[3]	Formulation B	Formulation C
Cabotegravir[1]	(b) (4)	200.0	200.0	(b) (4)
Mannitol		35.0	35.0	
Polysorbate 20		20.0	20.0	
Polyethylene glycol (PEG) 3350		20.0	20.0	
(b) (4)				
Water for Injection	q.s.	q.s.	q.s.	q.s.
(b) (4)				
Clinical study number(s)	LAI114433 LAI115428	LAI116815[4] *200056* *201120* *201103*	LAI116815[4]	LAI116815[4]
Doses administered (mg)	200 – 800	400 – 800	400	400

Notes:
1. (b) (4)
2.
3. Phase 2 studies that used Formulation A are italicized
4. Phase 1 relative bioavailability study

Formulation A was also used in Phase 2 clinical studies. Formulations A, B, and C were used in a relative bioavailability study LAI116815 and showed that:

- [redacted] (b) (4)
- Formulations A, B, and C resulted in a similar concentration 12 weeks post-injection. Although [redacted] (b) (4) .

Therefore, [redacted] (b) (4) was selected for Phase II studies as it was used in all previous clinical studies and, therefore, viewed as the option to most reliably provide adequate exposures. Following successful Phase 2 clinical studies, Formulation A was progressed into Phase 3 clinical studies and is the proposed commercial formulation. The proposed commercial formulation composition (Formulation A) and manufacturing site are identical to that of the drug product used in the Phase 3 clinical studies, therefore, bridging is not needed.
Two fill presentations/vials, 2-mL, and 3-mL, to provide a dose of 400 mg/2 mL and 600 mg/3 mL, respectively, of Formulation A are proposed for commercialization [redacted] (b) (4) was used for the manufacture of supplies for Phase 1 and Phase 2 Studies. The [redacted] (b) (4) to support Phase 3 clinical trials.

Assessment: ***Adequate*** The proposed commercial formulation composition (Formulation A) and manufacturing site are identical to that of the drug product used in the Phase 3 clinical studies, therefore, bridging is not needed.

B. 5 BIOWAIVER REQUEST

Assessment: ***None***

R. REGIONAL INFORMATION

Comparability Protocols

Assessment: ***None***

Post-Approval Commitments

Assessment: ***None***

Lifecycle Management Considerations

None

BIOPHARMACEUTICS LIST OF DEFICIENCIES

None

Primary Biopharmaceutics Assessor's Name and Date:
Akm Khairuzzaman, Ph.D., 10/17/2019

Secondary Assessor Name and Date (and Secondary Summary, as needed):
Elsbeth Chikhale, Ph.D., 10/17/2019

Akm Khairuzzaman

Digitally signed by Akm Khairuzzaman
Date: 11/04/2019 08:52:08AM
GUID: 502d1ab500002aef5afaa6f74ddf7e69

Elsbeth Chikhale

Digitally signed by Elsbeth Chikhale
Date: 11/12/2019 08:06:58AM
GUID: 50743ccc000031928b54eba1769a5df9

OFFICE OF DEVICE EVALUATION

DIVISION OF ANESTHESIOLOGY, GENERAL HOSPITAL, RESPIRATORY, INFECTION CONTROL, AND DENTAL DEVICES

INTERCENTER CONSULT MEMORANDUM

Instructions | Submission Information

Date	10/28/2019		
To:	Andrew Gentles		
Requesting Center/Office:	CDER/OND	**Clinical Review Division:**	OAP/DAVP
From	Kathleen Fitzgerald CDRH/OPEQ/OHT3/DHT3C/THT3C3		
Through (Team Lead)	Rumi Young,Combination Products Team Lead Injection Team CDRH/OPEQ/OHT3/DHT3C/THT3C1		
Through (Branch Chief)	CPT Alan Stevens, Branch Chief CDRH/ OPEQ/OHT3/DHT3C/THT3C1		
Subject	NDA 212888 , Cabotegravir LA + Rilpivirine LA injectable ICC1900382 Syringe, Safety Needle and Vial Adaptor		
Recommendation	**Filing Recommendation Date:** Click or tap to enter a date. ☐ CDRH did not provide a Filing Recommendation ☑ Device Constituent Parts of the Combination Product are acceptable for Filing. ☐ Device Constituents Parts of the Combination Product are Acceptable for Filing with Information requests for the 74-Day Letter, See Appendix A ☐ Device Constituents Parts of the Combination Product are Not Acceptable for Filing - See Section 5 for Deficiencies		
	Mid-Cycle Recommendation Date: 9/20/2019 ☐ CDRH did not provide a Mid-Cycle Recommendation ☐ CDRH has no approvability issues at this time. ☑ CDRH has additional Information Requests, See Appendix A ☐ CDRH has Major Deficiencies that may present an approvability issue, See Appendix A.		
	Final Recommendation Date: 10/28/2019 ☑ Device Constituent Parts of the Combination Product are Approvable. ☐ Device Constituent Parts of the Combination Product are Approvable with Post-Market Requirements/Commitments, See Section 2.3 ☐ Device Constituent Parts of the Combination Product are Not Approvable - See Section 2.2 for Complete Response Deficiencies		

Digital Signature Concurrence Table

Reviewer	Team Lead (TL)	Assistant Director or Branch Chief (AD/BC)

Remove Buttons

1. SUBMISSION OVERVIEW

Submission Information	
Submission Number	NDA 212888
Sponsor	ViiV HealthCare
Drug/Biologic	Cabotegravir LA + Rilpivirine LA injectable
Indications for Use	Treatment of HIV-1 infection
Device Constituent	Syringe, Safety Needle and Vial Adaptor
Related Files	ICC1600651, ICC1600684, ICC1700368, ICC1700816 and ICC1801005

Review Team		
Lead Device Reviewer	Kathleen Fitzgerald	
The CDRH review is being managed under ICC #: ICC1900382 Below is a list of the Discipline Specific CON#.		
Discipline Specific Consults	**Reviewer Name (Center/Office/Division/Branch)**	**CON #**
None		

Important Dates	
Discipline-Specific Review Memos Due	N/A
Final Lead Device Review Memo Due	November 1, 2019

2. EXECUTIVE SUMMARY AND RECOMMENDATION

CDRH recommends the combination product is:

☑ Approvable – the device constituent of the combination product is approvable for the proposed indication.
☐ Approvable with PMC or PMR, See Section 2.3
☐ Not Acceptable – the device constituent of the combination product is not approvable for the proposed indication for the following reasons : . We have Major Deficiencies to convey, see Section 2.2.

Section	Adequate			Reviewer Conclusions
	Yes	No	NA	
Device Description	X			
Design Controls	X			
Risk Analysis	X			
Design Verification	X			
Consultant Discipline Reviews			X	
Clinical Validation	X			
Human Factors Validation			X	Reviewed by DMEPA
Labeling	X			
Quality Systems/ Manufacturing Controls	X			

2.1. Comments to the Review Team

☑ CDRH does not have any further comments to convey to the review team.
☐ CDRH has the following comments to convey to the review team:

2.2. Complete Response Deficiencies

☑ There are no outstanding unresolved information requests, therefore CDRH does not have any outstanding deficiencies.
☐ The following outstanding unresolved information requests should be communicated to the Sponsor as part of the CR Letter:

2.3. Recommended Post-Market Commitments/Requirements

CDRH has Post-Market Commitments or Requirements	☐
CDRH does not have Post-Market Commitments or Requirements	☑

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3. PURPOSE/BACKGROUND

3.1. Scope

ViiV HealthCare is requesting approval of Cabotegravir LA + Rilpivirine LA injectable. The device constituent of the combination product is a Syringe, Safety needle and Vial adaptor.

Choose an item. has requested the following consult for review of the device constituent of the combination product:

NDA 212888 (Cabenuva, cabotegravir LA + rilpivirine LA injectable co-pack) is to be used as a once-monthly injection in pts with HIV-1 infection. The injectable product is supplied as a combination product co-pack. The pack includes 1 single-dose vial of cabotegravir, 1 single-dose vial of rilpivirine, 2 vial adapters, 2 syringes, 2 injection needles and instructions for use. Please review the device constituent parts of this application.

The goal of this memo is to provide a recommendation of the approvability of the device constituent of the combination product. This review will cover the following review areas:

Device constituent parts of the co-pack kit combination product for device compatibility and functional performance.

This review will not cover the following review areas:

Drug product or the primary container closure vial.

The original review division will be responsible for the decision regarding the overall safety and effectiveness for approvability of the combination product.

3.2. Prior Interactions

3.2.1. Related Files

ICC1600651, ICC1600684, ICC1700368, ICC1700816 and ICC1801005

3.3. Indications for Use

Combination Product	Indications for Use
Cabotegravir LA + Rilpivirine LA injectable	Treatment of HIV-1 infection
Syringe, Safety needle and Vial Adaptor	Delivery of the Drug Product

4. DEVICE DESCRIPTION

DEVICE DESCRIPTION REVIEW SUMMARY/CONCLUSION		
Filing Deficiencies: ☐ **Yes** ☑ **No** ☐ **N/A**	**Mid-Cycle Deficiencies:** ☑ **Yes** ☐ **No** ☐ **N/A**	**Final Deficiencies:** ☐ **Yes** ☑ **No** ☐ **N/A**
Reviewer Conclusion Mid-Cycle Comments:		

Final Review Comments: The Sponsor has provided complete device description information. All the device constituest parts are 510(k) cleared and the LOAs were provided.

Materials Reviewed	
Document Title	**Location**
NDA 212888	3.2.R

4.1. Device Description

Select Device Type:				
	☐ Auto-Injector ☐ Infusion Pump ☐ Metered-Dose Pump	☐ Nasal Spray ☐ Oral Syringe ☐ Pen-Injector	☐ Prefilled Syringe ☐ Subdermal Implant Kits ☑ Vial adapters	☑ Other

Two co-pack kits have been developed in order to accommodate the dosing regimen. The co-packs are described as (b) (4) and (b) (4)', in alignment with the injection volume common to both products in each co-pack.

APPEARS THIS WAY ON ORIGINAL

Co-Pack	Drug Product Constituent Parts	Device Constituent Parts		
(b) (4)	(1) Vial of Cabotegravir Injectable Suspension, 400 mg/2 mL (1) Vial of Rilpivirine Extended-release Suspension for Injection, 600 mg/2 mL	(2) Sterile single-use vial adapters	(2) Sterile 5-mL single-use syringes	(2) Sterile single-use 23-gauge 1.5-inch safety needles
(b) (4)	(1) Vial of Cabotegravir Injectable Suspension, 600 mg/3 mL (1) Vial of Rilpivirine Extended-release Suspension for Injection, 900 mg/3 mL	(2) Sterile single-use vial adapters	(2) Sterile 5-mL single-use syringes	(2) Sterile single-use 23-gauge 1.5-inch safety needles

Vial Adapter

Syringe

Safety Needle

Figure 1 Co-Pack Images – (b) (4)

(b) (4)

	Tradename and Identifier	Description	Material of Construction (Product Contact)	Packaging	Manufacturer	Device Classification	510(k) Reference	Reference
Vial Adapter	Vial Adapter (b) (4)	Sterile, single-use, 13 mm vial adapter with an integrated luer connection	Body: (b) (4)	Single pre-packaged in (b) (4) blister pack with (b) (4) lid, (b) (4) labelled with shelf-life	(b) (4)	Class II Set, I.V. Fluid Transfer	(b) (4)	3.1.1
Syringe	(b) (4)	Sterile, single-use, 5 mL syringe	Barrel & Plunger: (b) (4) Plunger Gasket: (b) (4)	Single pre-packaged blister pack, (b) (4) labelled with shelf-life	(b) (4)	Class II Piston Syringe	(b) (4)	3.1.2
Safety Needle	(b) (4)	Sterile, single-use, 23G 1.5-inch safety needle	Cannula: Stainless steel Safety Sheath: (b) (4)	Single pre-packaged blister pack, (b) (4) labelled with shelf-life	(b) (4)	Class II Needle, (b) (4) (b) (4)	(b) (4)	3.1.3

Vial Adapter- The vial adapter is a fluid transfer device that facilitates the withdrawal of liquid drug products from vials into syringes for dosing, without coring or fragmentation of the rubber stopper. The vial adapter has an integrated plastic spike on the 'vial end' and luer fitting on the 'syringe end'. Once attached onto the vial, the spike punctures the stopper, and the drug product can be aspirated by attaching a luer syringe onto the luer fitting and pulling back the syringe plunger. The fluid contact path is sterile.

5ml Syringe- Two sterile single-use 5-mL syringes are included in each co-pack to enable aspiration and administration of the two-drug injectable dosing regimen. The syringe is graduated in alignment with the dosing requirements. The syringe has an integrated plastic luer fitting for connection to the vial adapter (for aspiration) and needle (for administration).

Safety Needle- Two sterile single-use 23G 1.5-inch safety needles are included in each co-pack to enable administration of the two-drug injectable dosing regimen. The safety needle is a needle with an attached plastic sheath which functions as a sharps injury prevention feature. After use of the needle for injection of the drug product, the needle is locked into the sheath via manual activation, which prevents sharps exposure after dosing is completed. The needle has an integrated plastic luer fitting for connection to the syringe.

4.2. Steps for Using the Device

The Instructions for Use (IFU) enclosed in the kit includes the instructions to be used by the HCP in the preparation and administration of each drug product in the two drug injectable dose regimen. A summary of the instructions follows:

1 Page of Draft Labeling has been Withheld in Full as b4 (CCI/TS) immediately following this page

4.3. Device Description Interactive Review

CDRH sent Device Description Interactive Review Questions to the Sponsor	☐ **Yes** ☑ **No**

Add Additional Information Request

5. FILING REVIEW

CDRH performed Filing Review	☑
CDRH was not consulted prior to the Filing Date; therefore CDRH did not perform a Filing Review	☐

FILING REVIEW SUMMARY/CONCLUSION	
Acceptable for Filing: ☑ **Yes** ☐ **No** ☐ **N/A**	**74-Day Letter or RTF Deficiencies:** ☐ **Yes** ☐ **No** ☑ **N/A**
Facilities Inspection Recommendation: ☐ **(PAI) Pre-Approval Inspection** ☐ **Post-Approval Inspection** ☐ **Routine Surveillance** ☑ **No Inspection** **Site(s) needing inspection:**	

Reviewer Conclusion
Refuse to File Deficiencies -None **74-Day Letter Deficiencies:None**

Filing Review Checklist				
Description		**Present**		
		Yes	**No**	**N/A**
Description of Device Constituent		X		
Device Constituent Labeling		X		
Letters of Authorization		X		
Essential Performance Requirements defined by the application Sponsor		X		
Design Requirements Specifications included in the NDA / BLA by the application Sponsor		X		
Design Verification Data included in the NDA / BLA or adequately cross-referenced to a master file.		X		
Risk Analysis supplied in the NDA / BLA by the application Sponsor		X		
Traceability between Design Requirements, Risk Control Measures and V&V Activities		X		
Verification/ Validation Check	Full Test Reports for Verification and Validation Testing	X		
	Engineering Performance (must include Safety Assurance Case for Infusion Pumps)	X		
	Reliability	X		
	Biocompatibility-completed in 510k review			X
	Sterility -completed in 510k review			X
	Software			X
	Cybersecurity			X
	Electrical Safety			X
	EMC/RF Wireless			X
	MR Compatibility			X
	Human Factors	X		
	Shelf Life, Aging and Transportation	X		
	Clinical Validation	X		
	Human Factors Validation			X
Quality Systems/ Manufacturing Controls Check	Description of Device Manufacturing Process	X		
	Description of Quality Systems (Drug cGMP-based, Device QSR-based, Both)	X		
	CAPA Procedure	X		
	Control Strategy provided for EPRs	X		

Reviewer Comment
The applicant has provided adequate device constituent documentation for filing.

5.1. Facilities Information

NO CDRH Quality Systems or Facilities review required.

All of the device constituent parts are 510(k) cleared and are well understood with basic technology and have a low-risk of device related injuries or malfunction.

5.2. Filing Review Interactive Review

CDRH sent Interactive Filing Review Questions to the Sponsor	☐ Yes ☑ No

Add Additional Information Request

6. DESIGN CONTROL SUMMARY

DESIGN CONTROL REVIEW SUMMARY/CONCLUSION		
Filing Deficiencies: ☐ Yes ☑ No ☐ N/A	**Mid-Cycle Deficiencies:** ☐ Yes ☑ No ☐ N/A	**Final Deficiencies:** ☐ Yes ☑ No ☐ N/A
Reviewer Conclusion Mid-Cycle Comments:No deficiencies. Final Review Comments: The Sponsor has provided adequate information.		

Materials Reviewed	
Document Title	**Location**
NDA 212888	3.2R, 3.2.P.2.2

6.1. Summary of Design Control Activities

Risk Analysis Attributes	**Yes**	**No**	**N/A**
Risk analysis conducted on the combination product	**X**		
Hazards adequately identified (e.g. FMEA, FTA, post-market data, etc.)	**X**		
Mitigations are adequate to reduce risk to health	**X**		
Version history demonstrates risk management throughout design / development activities	**X**		
Design Inputs/Outputs	**Yes**	**No**	**N/A**
Design requirements / specifications document present (essential performance requirements included)			
Design Verification / Validation Attributes	**Yes**	**No**	**N/A**
Validation of essential requirements covered by clinical and human factors testing	X		
To-be-marketed device was used in the pivotal clinical trial		X	
Bioequivalence Study utilized to-be-marketed device	X		
Verification methods relevant to specific use conditions as described in design documents and labeling	X		
Device reliability is acceptable to support the indications for use (i.e. emergency use combination product may require separate reliability study)	X		
Traceability demonstrated for specifications to performance data	X		

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(b) (4)

[redacted]

6.4. Design Control Interactive Review

CDRH sent Design Control Interactive Review Questions to the Sponsor	☐ Yes ☑ No

Add Additional Information Request

7. RISK ANALYSIS

RISK ANALYSIS REVIEW SUMMARY/CONCLUSION		
Filing Deficiencies: ☐ Yes ☑ No ☐ N/A	**Mid-Cycle Deficiencies:** ☐ Yes ☑ No ☐ N/A	**Final Deficiencies:** ☐ Yes ☑ No ☐ N/A
Reviewer Conclusion Mid-Cycle Comments: Final Review Comments:		

Materials Reviewed	
Document Title	**Location**
NDA 212888	3.2.R-Risk assessment

7.1. Risk Management Plan

The device constituent parts in the co-pack kit combination product will be prepared and the medication administered by a healthcare professional. They are well know, commonly used devices with low risks. The Sponsor provided the following risk assessment of using the device constituent parts incorrectly.

Risk acceptance matrix								
	None	Discomfort	Minor	Medical Attention	Permanent	Life threat	Not known	
Improbable	A	A	A	A	A	A	A	
Unlikely	A	A	A	A	A	U1	K/G	
Remote	A	A	A	A	U1	U2	K/G	
Occasional	A	A	A	U1	U2	U3	K/G	
Probable	A	A	U1	U2	U3	U4	K/G	
Frequent	A	U1	U2	U3	U4	U5	K/G	
Not known	A	K/G	K/G	K/G	K/G	K/G	K/G	

Term	Definition
A	Risk acceptable.
U1 to U5	Risk unacceptable. Will require risk benefit-justification after the exhaustion of all risk mitigation strategies
K/G	Risk unacceptable due to lack of knowledge. Further work required to understand risk

Reviewer Comments -The risk assessment of the device consitiuent parts was based on the human factors study. The applicants risk assessment is adequate**.**

7.2. Hazard Analysis and Risk Summary Report

Risk Summary of device constituent parts:

ID	Process Step	Cause of failure	Chain of events	Effect (Hazard)	*Severity*	*Occurrence*	Existing controls (justification for occurrence score)	Risk Level
							the dose, and to check that a full dose has been draw prior to injection.	
17	Preparation of vials	Failure to clean top of vial with alcohol swab	Microbial contamination of product	Delivery of non sterile dose	Medical Attention	Unlikely	Limited time for microbial growth between vial preparation and delivery	A
18	Transfer of dose to syringe	Spike breakage	Unable to transfer medicine to syringe	CAB Failure to deliver effective dose (once)	Medical Attention	Improbable	Not seen on the 13mm vial adaptor in any HF studies.	A
19	Transfer of dose to syringe	Spike breakage	Unable to transfer medicine to syringe	RPV Failure to deliver effective dose (once)	Medical Attention	Improbable	Not seen on the 13mm vial adaptor in any HF studies.	A
20	Transfer of dose to syringe	Spike cause leakage path in septum	Cabotegravir leakage onto skin	Cabotegravir Dermal exposure	None	Unlikely	HCP should be wearing gloves. IFU states gloves required.	A
21	Transfer of dose to syringe	Spike cause leakage path in septum	Rilpivirine leakage onto skin	RPV Dermal contact	None	Unlikely	HCP should be wearing gloves.	A
22	Transfer of dose to syringe	Spike cause leakage path in septum	Cabotegravir loss of drug product	CAB Failure to deliver effective dose (once)	Medical Attention	Unlikely	HF studies show this is not an issue	A
23	Transfer of dose to syringe	Spike cause leakage path in septum	Rilpivirine loss of drug product	RPV Failure to deliver effective dose (once)	Medical Attention	Unlikely	HF studies show this is not an issue	A
24	Transfer of dose to syringe	Drop component	Component breaks	CAB Failure to deliver effective dose (once)	Medical Attention	Unlikely	Stock of products available at treatment centre. Off the shelf components used. Possibility to use other needles, this does not affect PK data	A
25	Transfer of dose to syringe	Drop component	Component breaks	RPV Failure to deliver effective dose (once)	Medical Attention	Unlikely	Stock of products available at treatment	A

							centre. Off the shelf components used. Possibility to use other needles, this does not affect PK data	
26	Transfer of dose to syringe	Failure to inject air into vial	More difficult to transfer dose to syringe	CAB Failure to deliver effective dose (once)	Medical Attention	Remote	(b) (4) IFU provided. HCP should check dose before injecting. HF studies show that this is not an issue.	A
27	Transfer of dose to syringe	Failure to inject air into vial	More difficult to transfer dose to syringe	RPV Failure to deliver effective dose (once)	Medical Attention	Remote	(b) (4) IFU provided. HCP should check dose before injecting. HF studies show that this is not an issue.	A
28	Transfer of dose to syringe	Back pressure in vial	Syringe is filled, not disconnected from vial adaptor for some time, back pressure reduces volume in syringe, syringe dose not checked before injection, lower volume delivered	CAB Failure to deliver effective dose (multiple times)	Permanent	Unlikely	(b) (4) IFU provided and has been updated to state that HCP should check the syringe before administering the dose.	A
29	Transfer of dose to syringe	Back pressure in vial	Syringe is filled, not disconnected from vial adaptor for some time, back pressure reduces volume in syringe, syringe dose not checked before injection, lower volume delivered	RPV Failure to deliver effective dose (multiple times)	Permanent	Unlikely	(b) (4) IFU provided and has been updated to state that HCP should check the syringe before administering the dose.	A
30	Prepare syringe	Incorrect attachment of needle	Leakage or jetting during delivery	Cabotegravir Dermal exposure	None	Remote	(b) (4) Standard luer lock	A

31	Prepare syringe	Incorrect attachment of needle	Leakage or jetting during delivery	RPV Dermal contact	None	Remote	(b) (4) Standard luer lock components being used.	A
32	Prepare syringe	Incorrect attachment of needle	Leakage or jetting during delivery	Cabotegravir Mucus membrane exposure	Discomfort	Remote	(b) (4) Standard luer lock components being used.	A
33	Prepare syringe	Incorrect attachment of needle	Leakage or jetting during delivery	RPV Ocular contact	Discomfort	Remote	(b) (4) Standard luer lock components being used.	A
34	Prepare syringe	Incorrect attachment of needle	Leakage or jetting during delivery	CAB Failure to deliver effective dose (once)	Medical Attention	Unlikely	(b) (4) Standard luer lock components being used. Not	A
35	Prepare syringe	Incorrect attachment of needle	Leakage or jetting during delivery	RPV Failure to deliver effective dose (once)	Medical Attention	Unlikely	(b) (4) Standard luer lock components being used. Not seen as an issue during HF tests.	A
36	Prepare syringe	Syringe prepared too early	Sedimentation in syringe failure to deliver dose	RPV Failure to deliver effective dose (once)	Medical Attention	Unlikely	(b) (4) Sedimentation expected to take over 2 hours	A
37	Prepare syringe	Syringe prepared too early	Sedimentation in syringe failure to deliver dose	CAB Failure to deliver effective dose (once)	Medical Attention	Unlikely	(b) (4) Sedimentation expected to take over 2 hours	A
38	Prepare syringe	Syringe prepared too early	Exposure to light (Rilpivirine)	RPV delivery of degraded drug	Permanent	Improbable	IFU provided. Pack has closable lid feature. Injection should happen shortly after being drawn into syringe. As advised by (b) (4)	A

APPEARS THIS WAY ON ORIG NAL

							(b) (4)	
39	Dose delivery	Incorrect injection depth	Dose delivered subcutaneously	Cabotegravir Dose delivered subcutaneously	Minor	Occasional	(b) (4)	A
40	Dose delivery	Incorrect injection depth	Dose delivered subcutaneously	RPV Subcutaneous injection	Minor	Occasional	(b) (4)	A
41	Dose delivery	Failure to aspirate before injecting	Injection into blood vessel	Cabotegravir Dose delivered intravenously	Permanent	Unlikely	(b) (4)	A
42	Dose delivery	Failure to aspirate before injecting	Injection into blood vessel	RPV Intravenous injection	Permanent	Unlikely		A
43	Dose delivery	Injection into dorsogluteal site	Injection in dorsogluteal site, incorrect techniques used, sciatic nerve hit	Nerve damage from injection	Permanent	Unlikely	Instructions state ventrogluteal site injection is preferred. Injury to sciatic nerve unlikely due to training. Dorsogluteal site is still safe if correct technique used.	A
44	Disposal	Fail to activate needle safety system	Failure to put used needle into sharps bin. Non-patient receives contaminated needle stick injury	Cross contamination	Permanent	Unlikely	Most HCPs activated the safety after use and all disposed of in sharps bin.	A

45	Disposal	Wrong technique used to activate needle safety system	HCP receives contaminated needle stick injury	Cross contamination	Permanent	Unlikely	(b) (4) (b) (4) In HF tests when unsure they just disposed of used needle into the sharps bin. Needle safety system is compliant with ISO standard.	A
46	Dose delivery	Dose delivered orally	Syringe used as a dosing syringe and dose delivered orally	Cabotegravir Oral exposure	Discomfort	Improbable	(b) (4) IFU provided.	A
47	Dose delivery	Dose delivered orally	Syringe used as a dosing syringe and dose delivered orally	CAB Failure to deliver effective dose (multiple times)	Permanent	Improbable	(b) (4) IFU provided.	A
48	Dose delivery	Dose delivered orally	Syringe used as a dosing syringe and dose delivered orally	RPV Oral dose	Discomfort	Improbable	(b) (4) IFU provided.	A
49	Dose delivery	Dose delivered orally	Syringe used as a dosing syringe and dose delivered orally	RPV Failure to deliver effective dose (multiple times)	Permanent	Improbable	(b) (4) IFU provided.	A
50	Transfer of dose to syringe	Use needle rather than vial adaptor for dose transfer	Needle becomes blunted	Injection with blunted needle	Discomfort	Unlikely	(b) (4) IFU provided.	A
51	Transfer of dose to syringe	Drawing up from both vials	Confusion over treatment and HCP attempts to mix the products	CAB Failure to deliver effective dose (multiple times)	Permanent	Unlikely	Not seen in HF or clinical studies. (b) (4) HCP should be aware of the treatment.	A
52	Transfer of dose to syringe	Drawing up from both vials	Confusions over treatment and HCP attempts to mix the products	RPV Failure to deliver effective dose (multiple times)	Permanent	Unlikely	Not seen in HF or clinical studies. (b) (4) HCP should be aware of the treatment.	A
53	Prepare syringe	Inadequate needle used	Too short a needle used results in subcutaneous injection of CAB	Cabotegravir Dose delivered subcutaneously	Minor	Unlikely	(b) (4) Not seen in the Clinical Trials. Needles are provided within	A

							the pack given to HCP.	
54	Prepare syringe	Inadequate needle used	Too short a needle used results in subcutaneous injection of RPV	RPV Subcutaneous injection	Minor	Unlikely	(b) (4) Not seen in the Clinical Trials. Needles are provided within the pack given to HCP.	A
55	Prepare syringe	Inadequate needle used	Large needle gauge used, suspension blocks needle	CAB Failure to deliver effective dose (once)	Medical Attention	Unlikely	(b) (4) Not seen in the Clinical Trials. Needles are provided within the pack given to HCP.	A
56	Prepare syringe	Inadequate needle used	Large needle gauge used, suspension blocks needle	RPV Failure to deliver effective dose (once)	Medical Attention	Unlikely	(b) (4) Not seen in the Clinical Trials. Needles are provided within the pack given to HCP.	A
57	Dose delivery	Injection into non patient	HCP accidental needle stick during needle insertion	Needlestick injury (Sterile)	Minor	Unlikely	(b) (4) Components have needle protection for after use. Not seen in any of the HF studies	A
58	Dose delivery	Injection into non patient	HCP accidental needle stick during needle insertion, and injects CAB	Cabotegravir Single dose delivered to non patient	Discomfort	Improbable	(b) (4) Components have needle protection for after use. Not seen in any of the HF studies	A
59	Dose delivery	Injection into non patient	HCP accidental needle stick during needle insertion, and injects RPV	RPV Delivery to non-patient	Minor	Improbable	(b) (4) Components have needle protection for after use. Not seen in any of the HF studies	A
60	Dose delivery	Patient with High BMI	Incorrect needle used, results in	Cabotegravir Dose delivered subcutaneously	Minor	Unlikely	Phase 3 studies have not noted this to date. IFU	A

			incorrect injection depth				advises HCP to be aware of this.	
61	Dose delivery	Patient with High BMI	Incorrect needle used, results in incorrect injection depth	RPV Subcutaneous injection	Minor	Unlikely	Phase 3 studies have not noted this to date. IFU advises HCP to be aware of this.	A
62	Supply and storage	Wrong pack selected	Maintenance rather than starter	CAB Failure to deliver effective dose (multiple times)	Permanent	Improbable	Not seen in HF studies	A
63	Supply and storage	Wrong pack selected	Maintenance rather than starter	RPV Failure to deliver effective dose (multiple times)	Permanent	Improbable	Not seen in HF studies	A
64	Supply and storage	Wrong pack selected	Starter rather than maintenance	Cabotegravir Overdose (2 vial of loading phase)	Minor	Unlikely	Not seen in HF studies	A
65	Supply and storage	Wrong pack selected	Starter rather than maintenance	RPV overdose	Minor	Unlikely	Not seen in HF studies	A
66	Supply and storage	User splits pack	Various scenarios	CAB Failure to deliver effective dose (multiple times)	Permanent	Unlikely	Combination product stated on packaging. IFU provided. Not common practice to break up drug product packs. Not seen in HF tests	A
67	Transfer of dose to syringe	Vial adaptor contacted	Vial adaptor spike or luer lock left out of packaging and becomes contaminated	Delivery of non sterile dose	Medical Attention	Unlikely	Minimal time for microbial growth. HCP should be wearing gloves. Correct procedure explained in IFU.	A
68	Transfer of dose to syringe	CAB mixed into RPV vial	HCP misunderstands, thinks that the vials need to be mixed together, HCP put CAB into the RPV vial to mix	CAB Failure to deliver effective dose (multiple times)	Permanent	Unlikely	IFU provided. Not seen in HF.	A

69	Preparation of vials	Drug expired	HCP does not check the expiry date and the expiry date has past leading to injection of ineffective dose	CAB Failure to deliver effective dose (once)	Medical Attention	Improbable	It has been observed through HF studies that HCP's always check the date and it is part of their training.	A
70	Preparation of vials	Drug expired	HCP does not check the expiry date and the expiry date has past leading to injection of ineffective dose	RPV Failure to deliver effective dose (once)	Medical Attention	Improbable	It has been observed through HF studies that HCP's always check the date and it is part of their training.	A
71	Dose delivery	Second injection not delivered	HCP fails to continue to the second injection of the treatment	CAB Failure to deliver effective dose (once)	Medical Attention	Unlikely	(b) (4) IFU states to continue to the second injection once the first is complete.	A
72	Dose delivery	Second injection not delivered	HCP fails to continue to the second injection of the treatment	RPV Failure to deliver effective dose (once)	Medical Attention	Unlikely	(b) (4) , IFU states to continue to the second injection once the first is complete.	A

Reviewer Comments – The risk analysis/assessment was complete and adequate.

7.3. Risk Analysis Interactive Review

CDRH sent Risk Analysis Interactive Review Questions to the Sponsor	☐ **Yes** ☑ **No**

Add Additional Information Request

8. DESIGN VERIFICATION REVIEW

DESIGN VERIFICATION REVIEW SUMMARY/CONCLUSION		
Filing Deficiencies: ☐ **Yes** ☑ **No** ☐ **N/A**	**Mid-Cycle Deficiencies:** ☑ **Yes** ☐ **No** ☐ **N/A**	**Final Deficiencies:** ☐ **Yes** ☑ **No** ☐ **N/A**

Reviewer Conclusion

Mid-Cycle Comments: 2 IRs were sent to the Sponsor on 9-20-19. See IRs and responses under section 13.2 of this memo.

Final Review Comments: The Sponsor has provided complete and adequate test reports/information.

Materials Reviewed	
Document Title	**Location**
NDA 212888	P.2.2 , P.2.6 and P.5.4

Insert the following Reviewer Section or Guide: (phase 2- coming)

☐ ~~Biocompatibility~~ ☐ ~~Software/Cybersecurity~~ ☐ ~~Sterility~~	☐ ~~EMC~~ ☐ ~~Electrical Safety~~ ☐ ~~RF/Wireless~~ ☐ ~~Reliability~~

8.1. Performance/Engineering Verification

8.1.1. Essential Performance Requirement Evaluation

Test	Acceptance Criteria	Sample Size (# of units)	Mean Result	Minimum - Maximum (Std. Deviation)	Overall Result
Leakage test for syringe-needle connection[1] (mm)	The plunger displacement remains less than or equal to (b) (4) mm when subjected to an injection force of (b) (4) N after attachment of the safety needle to the syringe.	30	0.040	(b) (4) (0.020)	Pass
Vial adapter attachment/detachment force (N)	The force required to attach the vial adapter onto the vial shall not exceed (b) (4) N.	30	25.62	(b) (4) (1.73)	Pass
	The force required to disconnect the vial adapter from the vial shall be greater than (b) (4) N when applied axially.	30	16.15	(b) (4) (1.97)	Pass
Unscrewing torque test (Nm)	The unscrewing torque required to disconnect the vial adapter from the syringe shall be equal to or greater than (b) (4) Nm as per (b) (4)	30	0.060	(b) (4) (0.006)	Pass
Separation force test (N)	The force required to separate the syringe from the vial adapter in the axial direction shall exceed (b) (4) N as per (b) (4)	30	165 N	(b) (4) (13)	Pass
Stress cracking test[1]	The syringe to vial adapter connection shall not break or leak when tested according to (b) (4) stress cracking.	30	No visual cracks observed after 48 hours	N/A	Pass
Unscrewing torque test (Nm)	The unscrewing torque required to disconnect the safety needle from the syringe shall be equal to or greater than (b) (4) Nm as per (b) (4)	30	0.074	(b) (4) (0.009)	Pass
Separation force test (N)	The force required to separate the syringe from the needle shall exceed (b) (4) N as per (b) (4)	30	58.8	(b) (4) (3.6)	Pass
Stress cracking test[1]	The syringe to needle connection shall not break or leak when tested according to (b) (4) stress cracking.	30	No visual cracks observed after 48 hours	N/A	Pass

Notes:

Table 5 Stress Cracking Test and Leakage Test Results Following Storage at 25°C/60% RH

Test	Acceptance Criteria	Sample Size (# of units)	Timepoint (months)			
			Initial	1.5	3	6
Syringe to Vial Adapter connection - Stress Cracking	No visual cracks shall be visible 48 hours after stress crack testing	30	Pass	Pass	Pass	Pass
Syringe to Needle connection - Stress Cracking	No visual cracks shall be visible 48 hours after stress crack testing	30	Pass	Pass	Pass	Pass
Syringe to Needle connection - Leakage test in use condition (simulation of injection)	Plunger displacement (b) (4) mm after 48 hours	30	Pass	Pass	Pass	Pass

Table 6 Injectability Force for Rilpivirine Extended-release Suspension for Injection Following Storage at 25°C/60% RH

Test	Acceptance Criteria	Sample Size (# of units)	Timepoint (months)	Mean Result	Minimum-Maximum (Std. Deviation)	Overall Result
Injection force (N) 2-mL fill presentation	Average injection force of each measurement (b) (4) N	30	Initial	15.6	(b) (4) (0.6)	Pass
			1.5	15.4	(0.7)	Pass
			3	15.7	(0.7)	Pass
			6	16.0	(0.7)	Pass
Injection force (N) 3-mL fill presentation	Average injection force of each measurement (b) (4) N	30	Initial	16.2	(0.8)	Pass
			1.5	15.2	(0.6)	Pass
			3	16.1	(0.6)	Pass
			6	14.9	(0.7)	Pass

Reviewer Comment
The design verification test reports are adequate. The Sponsor completed the functional performance tests that CDRH recommended inprevious communications. Indidvidual device components were tested and cleared under their 510k submissions.

8.1.2. Design Functional Requirements (DFR) Evaluation

Design Input	Design Output	Verification Method	Results/Deviations	Adequately Verified (Y/N)	Validated through Clinical, Human Factors or Other	Adequately Validated (Y/N/NA)
Dose Accuracy	Aligned to drug product specification for extractable volume	Compliance to (b) (4)	Delivered volume contents from syringe, 2ml and 3ml	Y	Y- Human Factors	Y
Absence of leakage	Aligned to drug product specification for extractable volume	Compliance to (b) (4)	No leakage	Y	Y-Human Factors	Y
Vial, Vial adaptor, syringe and needle compatibility	Aligned to drug product specification for extractable volume	Compliance to (b) (4)	All device constituent parts are compatible	Y	Y-Human Factors	Y
Injection Force	Less than (b) (4) N (max value)	Compliance to (b) (4)	(b) (4) N	Y	Y-Human Factors	Y

Table 8 Syringeability Data for Cabotegravir Injectable Suspension

Fill Presentation	Batch Number	Storage Condition	Time (months)	Syringeability		
				Breakloose Force (N)	Average Glide Force (N)	Maximum Glide Force (N)
Acceptance Criteria				NGT (b) (4)	NGT (b) (4)	NGT (b) (4)
2-mL	172405685	Initial	0	(b) (4)		
		40°C/75% RH	1			
			3			
3-mL	172406948	Initial	0			
		40°C/75% RH	1			
			3			

Insert Additional Design Verification Table

Reviewer Comment
Documentation supporting the validation of administration of the co-pack is provided in m3.2.R. Attachment Human Factors Validation.

8.2. Design Verification Interactive Review

CDRH sent Design Verification Interactive Review Questions to the Sponsor	☑ Yes ☐ No

	Date Sent:9-20-19	Date/Sequence Received:9-27-19
Information Request #1	You have not provided the lot release specifications for all the device constituent parts of your combination product. The lot release specifications should include all the essential performance requirements for the combination product. The essential performance requirements for the vial adapter, syringe and safety needle include: Dose Accuracy Break loose/Glide Force Vial/adapter compatibility Adapter/syringe compatibility	
Sponsor Response	See Sponsor's complete response under section 13.2 of this memo.	
Reviewer Comments	Adequate response, deficiency resolved.	
Response Adequate:	☑ **Yes** ☐ **No, See IR # Sent on {date}**	

	Date Sent:9-20-19	Date/Sequence Received:9-27-19
Information Request #2	Please provide traceability documentation. A traceability matrix should be provided to ensure 1) the design outputs are adequately verified to meet the design inputs and 2) the finished combination product is validated to meet the user needs. It is highly recommended that the Essential Performance Requirements (EPRs) are highlighted for ease of review.	
Sponsor Response	See Sponsor's complete response under section 13.2 of this memo.	
Reviewer Comments	Adequate response, deficiency resolved.	
Response Adequate:	☑ **Yes** ☐ **No, See IR # Sent on {date}**	

Add Additional Information Request

8.3. Discipline Specific Sub-Consulted Reviews

☑ No Additional Discipline Specific Sub-Consults were requested
☐ The following additional Discipline Specific Sub-Consults were requested:

Discipline -Specific Design Verification / Validation adequately addressed					
Discipline	**Consult needed**			**Consultant**	**Section**
	Yes	**No**	**N/A**		
Engineering (Materials, Mechanical, General)			X		
Biocompatibility			X		
Sterility			X		
Software / Cybersecurity			X		
Electrical Safety / EMC			X		
Human Factors			X		10
Clinical			X		

Insert Discipline Review Section

8.3.1. Insert Discipline Review

DISCIPLINE REVIEW SUMMARY/CONCLUSION		
Filing Deficiencies: ☐ Yes ☐ No ☒ N/A	**Mid-Cycle Deficiencies:** ☐ Yes ☐ No ☒ N/A	**Final Deficiencies:** ☐ Yes ☐ No ☒ N/A
Reviewer Conclusion Mid-Cycle Comments: No Consults. Final Review Comments: No Consults.		

Materials Reviewed	
Document Title	**Location**
N/A	

9. CLINICAL VALIDATION REVIEW

CLINICAL VALIDATION REVIEW SUMMARY/CONCLUSION		
Filing Deficiencies: ☐ Yes ☑ No ☐ N/A	**Mid-Cycle Deficiencies:** ☐ Yes ☑ No ☐ N/A	**Final Deficiencies:** ☐ Yes ☑ No ☐ N/A
Reviewer Conclusion Mid-Cycle Comments: Information was adequate. Final Review Comments: Information was adequate		

Materials Reviewed	
Document Title	**Location**
NDA 212888-Clinical studies	1.11

9.1. Review of Clinical Studies Clinical Studies

☐ There are no clinical studies for review
☑ There are clinical studies for review

The Sponsor used information gathered from the Phase 3 clinical study to determine what device constituent parts to use in the to be marketed co-pack kit. The following is a summary:

Table 2 Phase 3 Clinical Trials vs. Commercial Co-Pack

		Phase 3 Clinical Trials	Commercial Co-Pack
Initiation Dose	Dose[1]	600 mg/3 mL dose of Cabotegravir Injectable Suspension 900 mg/3 mL dose of Rilpivirine Extended-release Suspension for Injection	
	Vials	2 x 2-mL vials[2] of each suspension required to deliver the intended doses	Separate, single-use 3-mL vial of each suspension to deliver the intended doses included in the co-pack
Continuation Dose	Dose[1]	400 mg/2 mL dose of Cabotegravir Injectable Suspension 600 mg/2 mL dose of Rilpivirine Extended-release Suspension for Injection	
	Vials	Separate, single-use vial of each suspension to deliver the intended doses	Separate, single-use vial of each suspension to deliver the intended doses included in the co-pack
Vial adapters		Aspiration device (if applicable, typically a needle) sourced by clinical sites	Included in the co-pack
Syringes		Sourced by clinical sites	Included in the co-pack
Needles		Sourced centrally or locally	Included in the co-pack[3]

Notes:

A review of syringes and needles utilized for dosing in the Phase 3 ATLAS clinical study (Protocol 201585) of Cabotegravir Injection Suspension, 200 mg/mL and Rilpivirine 300 mg/mL Extended-release Suspension for Injection was completed in order to inform device selection for the commercial co-pack.

Syringe

The primary syringe attribute assessed as a design input was the materials of construction. Both glass and plastic syringes were utilized for dosing in clinical trials. In a representative sampling of Cabotegravir Injection Suspension, 200 mg/mL (n=1314) and Rilpivirine 300 mg/mL Extended-release Suspension for Injection (n=1313) injections, approximately 98.5% were delivered using a plastic syringe and approximately 1.5% were delivered with a glass syringe. Of the injections delivered with a glass syringe, greater than 70% were restricted to one country (non-US).

Needle

Needle attributes assessed as design inputs were the needle length and needle gauge. Needle length was evaluated for potential impact to exposure, as well as suitability to deliver an IM injection across the weight and body mass index (BMI) range of patients. Needle gauge was primarily considered in relation to syringeability and pain perception.

Needle length

In the Phase 3 ATLAS clinical study (Protocol 201585), needle lengths ranging from 1- inch to greater than 2-inch were utilized for dosing Cabotegravir Injection Suspension, 200 mg/mL (n=3488) and Rilpivirine 300 mg/mL Extended-release Suspension for Injection (n=3490) as presented in Table 3. The data indicated that

approximately 91% of the injections were dosed with [redacted]-inch needle. A 1.5-inch needle length was selected for the co-pack to administer both Cabotegravir Injection Suspension, 200 mg/mL and Rilpivirine 300 mg/mL Extended-release Suspension for Injection. The use of alternate needle lengths is permitted at the discretion of the HCP based on patient need.

Table 3 Needle Lengths Used for Injections

		Cabotegravir Injection Suspension, 200 mg/mL	Rilpivirine 300 mg/mL Extended-release Suspension for Injection
Subjects (n)		303	303
Injections (n)		3488	3490
Needle Length (in)	1 - < 1.5	147 (4%)	148 (4%)
	1.5 - < 2	3175 (91%)	3176 (91%)
	≥ 2	166 (5%)	166 (5%)

Needle gauge

In the Phase 3 ATLAS clinical study (Protocol 201585), needle gauges ranging from [redacted] were utilized for dosing Cabotegravir Injection Suspension, 200 mg/mL (n=3488), and needle gauges from [redacted] were utilized for dosing Rilpivirine 300 mg/mL Extended-release Suspension for Injection (n=3490). As presented in Table 4, needle gauges used ranged from [redacted] for both drug products. A needle gauge of 23G was selected for the co-pack to administer both Cabotegravir Injection Suspension, 200 mg/mL and Rilpivirine 300 mg/mL Extended-release Suspension for Injection.

Table 4 Needle Gauges used for Injections

		Cabotegravir Injection Suspension, 200 mg/mL	Rilpivirine 300 mg/mL Extended-release Suspension for Injection
Subjects (n)		303	303
Injections (n)		3488	3490
Needle Gauge	(b) (4)	7 (<1%)	10 (<1%)
		1409 (40%)	2018 (58%)
		117 (3%)	153 (4%)
		1335 (38%)	1307 (37%)
		0 (0%)	0 (0%)
		620 (18%)	2 (<1%)

Reviewer Comment
The Sponsor used information gathered in the phase 3 clinical study to determine what devices to use in their co-pack. The Sponsor followed CDRH's recommendations from previous communications and used 510(k) cleared devices and a needle with a safety feature in their to be marketed co-pack kit.

9.2. Clinical Validation Interactive Review

CDRH sent Design Validation Interactive Review Questions to the Sponsor	☐ Yes ☑ No

Add Additional Information Request

10. HUMAN FACTORS VALIDATION REVIEW

CDRH Human Factors Review conducted		☐
Human Factors deferred to DMEPA	Review Instructions	☑

11. LABELING

LABELING REVIEW SUMMARY/CONCLUSION

Filing Deficiencies: ☐ Yes ☑ No ☐ N/A	Mid-Cycle Deficiencies: ☐ Yes ☑ No ☐ N/A	Final Deficiencies: ☐ Yes ☑ No ☐ N/A

Reviewer Conclusion

Mid-Cycle Comments: The device labeling and instructions for use is complete and adequate.

Final Review Comments: The device labeling and instructions for use is complete and adequate.

Materials Reviewed	
Document Title	**Location**
NDA 212888	1.14.1,2 and 3

11.1. General Labeling Review

The labeling, including the device constituent labeling, user guides, patient information, prescriber information and all other labeling materials provided for review were reviewed to meet the following general labeling guidelines as appropriate:

Device Labeling Review Checklist	Adequate?		
	Yes	No	N/A
Indications for Use or Intended Use; including use environment(s); route(s) of administration for infusion, and treatment population.	X		
Drug name is visible on device constituent and packaging	X		
Device/Combination Product Name and labeling is consistent with the type of device constituent	X		
Prescriptive Statement/Symbol on device constituent	X		
Warnings	X		
Contraindications	X		
Instructions for Use	X		
Final Instructions for Use Validated through Human Factors	X		
Electrical Safety Labeling/Symbols			X
EMC Labeling/Symbols			X
Software Version Labeling			X
MRI Labeling/Symbols			X
RF/Wireless Labeling/Symbols			X

Reviewer Comments -The device labeling is complete and adequate.

11.2. Device Specific Labeling Review

5 Pages of Draft Labeling have been Withheld in Full as b4 (CCI/ TS) immediately following this page

Add Additional Information Request

12. QUALITY SYSTEMS/MANUFACTURING CONTROLS

CDRH Quality Systems Review conducted	☐
CDRH Quality Systems Review was not conducted	☑

NO CDRH Quality Systems or Facilities review required.

All of the device constituent parts are 510(k) cleared and are well understood with basic technology and have a low-risk of device related injuries or malfunction.

13. APPENDIX A (INFORMATION REQUESTS)

13.1. Filing/74-Day Information Requests

None

13.2. Mid-Cycle Information Requests

1. CDRH Question 1-sent on September 20, 2019

You have not provided the lot release specifications for all the device constituent parts of your combination product. The lot release specifications should include all the essential performance requirements for the combination product. The essential performance requirements for the vial adapter, syringe and safety needle include:

Dose Accuracy

Break loose/Glide Force Vial/adapter compatibility

Adapter/syringe compatibility

Sponsor's Response Received September 27, 2019:

Clarification of Essential Performance Requirements

Based on the Agency's recommendation (IND 109,678 Preliminary Meeting Comments, Pre-NDA Type B Meeting, 28 January 2019), the Sponsor designated the following Essential Performance Requirements (EPRs) for the Combination Product (hereafter referred to as co-pack)

- Dose Accuracy
- Absence of Leakage
- Device Compatibility

This information is presented in Section 4.2.1 of m3.2.R_Attachment_Devices of NDA 212888.

Break loose/Glide Force has not been designated as an EPR for this co-pack. The rationale is based on the fact that drug product is filled into the syringe at the point of use, and as such, the syringe is not subject to a peak break loose followed by a glide force as opposed to a drug product, such as a pre-filled syringe, where these forces may be impacted by the long-term storage of the drug product in the syringe.

Injection Force has also not been designated as an EPR for this co-pack. Rather, the appropriate injection force for this co-packed product is based on the force needed to expel each drug product from the respective syringe after the drug product has been withdrawn into the syringe.

While break loose/glide force is not an EPR for this product presentation, injection force has been verified during development. As presented in Section 4.2.2 of m3.2.R_Attachment_Devices, this has been considered as an additional performance requirement. Further detail is included in the Traceability Matrix requested in Question 2 of this Information Request.

Device Constituent Parts of the Co-Pack

The Sponsor confirms adequate controls are in place to ensure that the device

components of the co-pack demonstrate acceptable performance for the defined EPRs. These controls include testing performed by the Sponsor during development of the co- pack, as well as testing performed by the device manufacturers to ensure lot-to-lot consistency of the pre-packed, pre-sterilized medical devices.

The devices are sourced from their original manufacturers in their original (pre-sterilized) blister packaging, with manufacturer-provided information such as lot number and expiration date. The devices are independently registered and marketed as stand-alone devices. It is noted that in order for these devices to be used in the commercial clinical environment, where healthcare practitioners (HCP) may choose devices manufactured by alternate manufacturers to facilitate drug delivery for independently marketed drug products, conformance to international standards is utilized in order to ensure compatibility. The Sponsor has confirmed the intended use of the devices to include compliance with such applicable international standards (including ISO 80369 for the luer connections), as is detailed below in Table 1.

The Sponsor acknowledges its accountability for the inter-compatibility I usability of the constituents (i.e., devices together with drug products) as used to prepare and administer the drug products to patients, and as such has confirmed suitability through verification and validation testing, as well as a supplier audit program and incoming component specifications.

Control Strategy

(b) (4)

[redacted]

5 Pages have been Withheld in Full as b4 (CCI/TS) immediately following this page

Reviewer's Comments: The Sponsor has provide a complete and adequate response.

13.3. Interactive Information Requests

None

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

DAVID J CLAFFEY
11/26/2019 12:32:09 PM