

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

212950Orig1s000

PRODUCT QUALITY REVIEW(S)

RECOMMENDATION

<input checked="" type="checkbox"/> Approval
<input type="checkbox"/> Approval with Post-Marketing Commitment
<input type="checkbox"/> Complete Response

NDA 213983 Assessment #1

Drug Product Name	Rukobia (fostemsavir)
Dosage Form	Extended Release Tablet
Strength	600 mg
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	ViiV Healthcare
US agent, if applicable	GSK

Submission(s) Assessed	Document Date	Discipline(s) Affected
Original (1 st Rolling Submission)	Sept 24, 2019	All
Final Rolling Submission (CMC)	Dec 4, 2019	Quality
Amendment	Jan 8, 2020	Quality
Amendment	Jan 29, 2020	Quality
Amendment	Mar 10, 2020	Quality
Amendment	Mar 25, 2020	Quality
Amendment	Apr 27, 2020	Quality
Amendment	May 5, 2020	Labeling
Amendment	May 14, 2020	Quality
Amendment	May 22, 2020	Labeling

QUALITY ASSESSMENT TEAM

Discipline	Primary Assessment	Secondary Assessment
Drug Substance	Soumya (Shomo) Mitra	Ali Al Hakim
Drug Product & Labeling	Hailin (Sheena) Wang	Stephen Miller
Manufacturing	Mark Johnson	Pei-I Chu
Biopharmaceutics	Qi Zhang	Elsbeth Chikhale
Regulatory Business Process Manager	Shamika Brooks	
Application Technical Lead	Stephen Miller	

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
Various	III		(b) (4)	Adeq	See DP review	

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

Document	Application Number	Description
IND	73916	PreNDA communications; Clinical studies

2. CONSULTS

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

EXECUTIVE SUMMARY

[IQA NDA Assessment Guide Reference](#)

I. RECOMMENDATIONS AND CONCLUSION ON APPROVABILITY

NDA 212950 is recommended for APPROVAL from the product quality perspective.

II. SUMMARY OF QUALITY ASSESSMENTS

A. Product Overview

Rukobia (fostemsavir) Extended Release Tablets contain 600 mg of fostemsavir, as the tromethamine salt. Fostemsavir is a phosphate ester prodrug which is hydrolyzed to the active moiety, temsavir, by alkaline phosphatase in the gastrointestinal tract. Temsavir binds directly to the gp120 subunit within the HIV-1 envelope glycoprotein (gp160) and selectively inhibits the interaction between the virus and cellular CD4 receptors, thereby preventing both attachment and post-attachment steps required for viral entry into host cells. The NDA received a priority (rolling) review under Fast Track and Breakthrough Therapy Designation.

Proposed Indication(s) including Intended Patient Population	Treatment of HIV-1 infection in heavily treatment-experienced adults with multidrug-resistant HIV-1 infection failing their current antiretroviral regimen due to resistance, intolerance, or safety considerations.
Duration of Treatment	Chronic
Maximum Daily Dose	1200 mg/day
Alternative Methods of Administration	None

B. Quality Assessment Overview

Drug Substance: Adequate

Fostemsavir tromethamine a prodrug that is hydrolyzed to the active moiety, temsavir, which binds directly into the gp120 subunit within the HIV-1 envelope glycoprotein gp160 complex and prevents the initial interaction between the virus and cellular CD4 receptors. The applicant has provided acceptable control in their manufacturing process for the drug substance, and adequate in-process checks are in place for control of critical process parameters. The manufacturing process produces a

(b) (4)
Fostemsavir tromethamine has high aqueous solubility ((b) (4) mg/mL at pH (b) (4) and >250 mg/ mL from pH 3.7 to pH (b) (4)) and is very stable when protected from light. Satisfactory data

has been provided for adequate control (b) (4) with a specification limit of (b) (4) ppm (b) (4)

(b) (4) is included in the (b) (4) monitoring at the drug substance manufacturing facility. The attributes and acceptance criteria in the drug substance are adequate and are justified with the acquired manufacturing process knowledge of 34 representative batches manufactured (b) (4) (b) (4) Sufficient stability data under long-term and accelerated conditions has been provided and a retest period of (b) (4) months is justified as per ICH Q1E.

For additional details see Soumya (Shomo) Mitra's Drug Substance Review, below.

Drug Product: Adequate

RUKOBIA (fostemsavir) extended-release tablets are beige, oval, film-coated, biconvex tablets debossed with "SV 1V7" on one side, containing 600 mg of fostemsavir as 725 mg of fostemsavir tromethamine. The tablets are supplied as a bottle of 60 tablets, with one tablet taken twice daily. Inactive ingredients include hydroxypropyl cellulose and hypromellose, (b) (4) All excipients meet USP/NF compendial requirements. The drug product specification includes tests for assay, content uniformity, related substances, dissolution and microbial attributes to ensure the identity, strength, purity and quality of the drug product.

(b) (4)

(b) (4) The totality of evidence indicates that this (b) (4) has a very low potential to induce an immune response in an individual who is not already sensitized, and antigenicity (b) (4) (see Integrated Review of NDA 212950, Section 7.7). Based on these considerations, an acceptance criterion of NMT (b) (4) ppm for the (b) (4) in fostemsavir tablets provides an appropriate assurance of safety (see FDA Responses Aug 30, 2018 to IND 073916). An (b) (4) method was developed for monitoring the (b) (4) which has a limit of detection of (b) (4) ppm and a limit of quantitation of (b) (4) ppm. The overall risk mitigation strategy includes (b) (4) routine monitoring (b) (4)

as well as batch release testing for 20 consecutive production-scale batches of tablets. With these controls in place, (b) (4) production-scale batches of tablets had levels (b) (4) below (b) (4) ppm. (b) (4)

(b) (4) The overall risk mitigation strategy (b) (4) provides adequate assurance of safety both for patients taking fostemsavir tablets (b) (4) (see also Drug Substance and Manufacturing sections of this Executive Summary).

When stored in the selected HPDE bottle with induction seal and child-resistant closure, fostemsavir tablets exhibits good chemical stability as demonstrated (b) (4) on stability. Satisfactory results from 36 months long term stability data (at both 25°C/60% RH and 30°C/75% RH) for the primary stability batches, and 6 month long-term and accelerated stability data for the production batches, supports the proposed shelf-life of 24 months at the following labeled condition: Store at 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C and 30°C (59°F and 86°F) [See USP Controlled Room Temperature] (see discussion in amendment Apr 27, 2020).

(b) (4) proposed in the initial submission, were removed from the NDA (Jan 8, 2020 amendment) (b) (4)

For additional details see Hailin (Sheena) Wang's Drug Product Review, below.

Labeling: Adequate

Recommendations have been conveyed to OND for consideration during labeling revisions. For additional details, see Hailin (Sheena) Wang's Labeling Review, below.

Manufacturing: Adequate

The drug substance and drug product manufacturing facilities, and all supporting facilities, are acceptable for their respective intended operations based on inspectional history and demonstrated manufacturing, packaging, and testing capability. The Overall Manufacturing Inspection Recommendation is "Approve" as of May 22, 2020.

The manufacturing process for commercial production of fostemsavir extended-release tablets utilizes (b) (4) pharmaceutical unit operations (b) (4)

(b) (4) Each manufacturing unit operation was evaluated for its potential impact on product quality, and all unit operations were found to have a low level of risk on both intermediate and final drug product quality attributes. Satisfactory results from both in-process checks and from release tests suggest that the unit operations mentioned above were in control for drug product batches manufactured for both clinical studies and for commercial development. The overall control strategy is adequate to ensure consistent production of finished product capable of meeting pre-determined acceptance criteria. The NDA includes data from 3 batches manufactured at a commercial scale of (b) (4) kg ((b) (4) tablets) and from 3 earlier batches manufactured at (b) (4) kg scale. Commercial batch scale may be varied to meet production demands up to (b) (4) (relative to (b) (4) kg) provided appropriate validation data are available. The microbiological control strategy for the commercial product integrates cGMP controls of the manufacturing environment with microbiological testing (b) (4)

(b) (4) This control strategy is acceptable and provides an equivalent degree of assurance of microbiological quality of the commercial product compared to routine microbial limit testing of the product alone.

(b) (4) These approaches to risk mitigation are in accordance with Agency expectations, as conveyed in PreNDA communications (e.g., FDA Responses June 12, 2017 to IND 073916).

For additional details see Mark Johnson's Manufacturing Review, below.

Biopharmaceutics: Adequate

The tablet formulation contains (b) (4) (b) (4)

The Applicant's proposed dissolution specifications for batch release and stability testing, are based on the previously agreed upon dissolution "safe space" under IND 073916. The Applicant has revised the acceptance criterion for the 2 hours' time point to (b) (4) % from (b) (4) %, as per the FDA's recommendation during this review cycle:

Dissolution Method and Acceptance Criteria for Rukobia™ (fostemsavir) Extended Release Tablet, 600 mg				
Apparatus	Rotation Speed	Medium	Medium Volume/Temp	Acceptance Criteria
USP Apparatus 1 (Basket)	100 rpm	0.05 M phosphate buffer, pH 6.8	900 mL/37°C	2 hours: (b) (4) % 7 hours: (b) (4) % 24 hours: NLT (b) (4) %

The results of in vitro alcohol dose dumping testing indicate minimal influence of alcohol on the drug release, and no tendency towards dose-dumping. Less drug is released from the proposed ER tablets with increasing amounts of alcohol but the difference in drug release profiles is insignificant (approximately <10% at each sampling time point and f2 >50) in 0.1 M HCl containing 0%, 5%, 20%, and 40% alcohol, and in pH 6.8 phosphate buffer containing 0%, 5%, 10%, and 20% alcohol.

All initial Phase 3 clinical batches and primary stability batches were manufactured at (b) (4) BMS, NJ. The GSK Parma, Italy facility was used for later clinical studies, and is the proposed manufacturing site of the commercial drug product. Per agreement under IND 073916 meeting dated November 27, 2017, a constructed dissolution "safe space", along with an f2 comparison in three different pH dissolution media, was used to demonstrate equivalency between tablets made at these manufacturing sites. The dissolution data for all three batches manufactured at the commercial site GSK Parma were within the defined dissolution "safe space" at all sampling time points. Additionally, the results of the comparative dissolution testing, i.e., with essentially overlapping dissolution profiles and f2 similarity values >75, show that the manufacturing site change did not significantly alter the drug release rates for the registration batches made at the commercial GSK

Parma site, compared to the Phase 3 batches made at (b) (4) BMS, thereby ensuring similar in-vivo performance of the extended-release tablets.

From the Biopharmaceutics perspective, the proposed drug product meets the “Extended-Release” claim based on the totality of the data/information, according to the criteria cited in 21 CFR 325.25(f).

For additional details see Qi Zhang’s Biopharmaceutics Review, below.

Microbiology (if applicable): Choose an item.

Not applicable. Microbiologic controls are covered in the Manufacturing review.

C. Risk Assessment

From Initial Risk Identification			Review Assessment		
Attribute/ CQA	Factors that can impact the CQA	Initial Risk Ranking	Risk Mitigation Approach	Final Risk Eval.	Lifecycle Considerations & Comments
Assay, Stability		L	(b) (4)	Acc	
Physical stability (solid state)	High solubility DS	L		Acc	
Content uniformity	(b) (4)	L		Acc	
Microbial limits		L		Acc	
Dissolution of Matrix System, e.g. Hydrophilic and hydrophobic matrix		M		Acc	
Alcohol dose dumping		H		Acc	
Patient Use Considerations		L		Acc	

D. List of Deficiencies for Complete Response – None / Not Applicable



Stephen
Miller

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Comments: ATL for NDA 212950

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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

RUKOBIA (fostemsavir) extended-release tablets, for oral use

Initial U.S. Approval: xxxx

Item	Information Provided in the NDA	Assessor's Comments
Product Title in Highlights		
Proprietary name	RUKOBIA	Adequate Proprietary name granted on 2/10/2020
Established name(s)	(fostemsavir) extended-release tablets	Adequate Active moiety used for the established name which is consistent with USP salt policy. Extended release designation is deemed acceptable per Biopharm reviewer Qi Zhang.
Route(s) of administration	For oral use	Adequate
Dosage Forms and Strengths Heading in Highlights		
Summary of the dosage form(s) and strength(s) in metric system.	Extended-release tablets: 600 mg	Adequate
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	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	N/A

1.2 FULL PRESCRIBING INFORMATION

1.2.1 Section 2 (DOSAGE AND ADMINISTRATION)

The recommended dosage of RUKOBIA is one 600-mg tablet taken orally twice daily with or without food [see *Clinical Pharmacology* (12.3)]. Swallow tablets whole. Do not chew, crush, or split tablets.

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)		Adequate from CMC perspective

1.2.2 Section 3 (DOSAGE FORMS AND STRENGTHS)

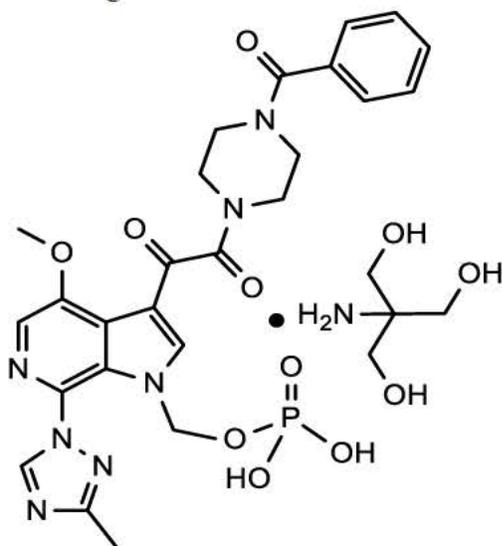
Each RUKOBIA extended-release tablet contains 600 mg of fostemsavir (equivalent to 725 mg of fostemsavir tromethamine). The tablets are beige, oval, film-coated, biconvex tablets, debossed with “SV 1V7” on one side.

Item	Information Provided in the NDA	Assessor’s Comments
DOSAGE FORMS AND STRENGTHS section		
Available dosage form(s)	Tablet	Adequate
Strength(s) in metric system	600 mg	Adequate
If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance	Each RUKOBIA extended-release tablet contains 600 mg of fostemsavir (equivalent to 725 mg of fostemsavir tromethamine).	Adequate
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting	The tablets are beige, oval, film-coated, biconvex tablets, debossed with “SV 1V7” on one side.	Adequate
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state “functionally scored”	N/A	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.	N/A	N/A

1.2.4 Section 11 (DESCRIPTION)

RUKOBIA (fostemsavir tromethamine) is a prodrug of temsavir, an HIV-1 attachment inhibitor.

The chemical name of fostemsavir tromethamine is (3-((4-benzoyl-1-piperazinyl)(oxo)acetyl)-4-methoxy-7-(3-methyl-1*H*-1,2,4-triazol-1-yl)-1*H*-pyrrolo[2,3-*c*]pyridin-1-yl)methyl dihydrogen phosphate, 2-amino-2-(hydroxymethyl)-1,3-propanediol (1:1). The empirical formula is C₂₅H₂₆N₇O₈P•C₄H₁₁NO₃. The molecular weight is 704.6 g/mol (583.5 as free acid). It has the following structural formula:

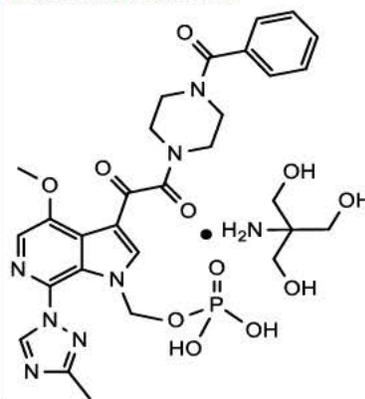


Fostemsavir tromethamine is a white powder and is soluble to greater than 250 mg/mL in aqueous solutions with a pH greater than 3.7.

RUKOBIA extended-release tablets are for oral administration. Each film-coated tablet contains 600 mg of fostemsavir (equivalent to 725 mg fostemsavir tromethamine), and the following inactive ingredients: colloidal silicon dioxide, hydroxypropyl cellulose, hypromellose, and magnesium stearate. The tablet film-coating contains the inactive ingredients iron oxide red, iron oxide yellow, polyethylene glycol, polyvinyl alcohol, talc, and titanium dioxide.

Item	Information Provided in the NDA	Assessor's Comments
DESCRIPTION section		
Proprietary and established name(s)	RUKOBIA extended-release tablets	Adequate
Dosage form(s) and route(s) of administration	Tablets for oral administration	Adequate
If the active ingredient is a salt, apply the USP Salt Policy and include the equivalency statement per FDA Guidance.	Each film-coated tablet contains 600 mg of fostemsavir (equivalent to 725 mg fostemsavir tromethamine)	Adequate The applicant adopted FDA recommended strength expression based on active moiety first, followed by

		equivalency statement to the active ingredient salt.
List names of all inactive ingredients. Use USP/NF names. Avoid Brand names.	the following inactive ingredients: colloidal silicon dioxide, hydroxypropyl cellulose, hypromellose, and magnesium stearate. The tablet film-coating contains the inactive ingredients iron oxide red, iron oxide yellow, polyethylene glycol, polyvinyl alcohol, talc, and titanium dioxide.	Adequate from CMC perspective Includes all excipients used for the tablet (b) (4) coating. Excipients are listed based on alphabetical order.
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	N/A
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	N/A	N/A
Statement of being sterile (if applicable)	N/A	N/A
Pharmacological/Therapeutic class	HIV-1 attachment inhibitor	Pharmacological/Therapeutic class is included. Recommend this edit to focus on the drug substance: (b) (4)
Chemical name, structural formula, molecular weight	(3-((4-benzoyl-1-piperazinyl)(oxo)acetyl)-4-methoxy-7-(3-methyl-1H-1,2,4-triazol-1-yl)-1H-pyrrolo[2,3-c]pyridin-1-yl)methyl dihydrogen phosphate, 2-amino-2-	Adequate Consistent with information provided in 3.2.S.

	<p>(hydroxymethyl)-1,3-propanediol (1:1). The empirical formula is C₂₅H₂₆N₇O₈P•C₄H₁₁NO₃. The molecular weight is 704.6 g/mol (583.5 as free acid). It has the following structural formula:</p> 	
If radioactive, statement of important nuclear characteristics.	N/A	N/A
Other important chemical or physical properties (such as pKa or pH)	Fostemsavir tromethamine is a white powder and is soluble to greater than 250 mg/mL in aqueous solutions with a pH greater than 3.7.	Adequate Consistent with information provided in 3.2.S.

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	N/A
Remove statements that may be misleading or promotional (b) (4)	... film-coating (b) (4) (b) (4)	Adequate The applicant adopted FDA recommended deletion (b) (4) (b) (4)

1.2.5 Section 16 (HOW SUPPLIED/STORAGE AND HANDLING)

1.1 How Supplied

RUKOBIA extended-release tablets, 600 mg, are beige, oval, film-coated, biconvex tablets debossed with "SV 1V7" on one side.

Bottle of 60 tablets with child-resistant closure. NDC 49702-250-18.

1.2 Storage

Store at 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C and 30°C (59°F and 86°F) [See USP Controlled Room Temperature].

RUKOBIA extended-release tablets may have a slight vinegar-like odor.

1.3 Handling

N/A

Item	Information Provided in the NDA	Assessor's Comments
HOW SUPPLIED/STORAGE AND HANDLING section		
Available dosage form(s)	RUKOBIA extended-release tablets	Adequate
Strength(s) in metric system	600 mg	Adequate
Available units (e.g., bottles of 100 tablets)	Bottle of 60 tablets	Adequate
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	beige, oval, film-coated, biconvex tablets debossed with "SV 1V7" on one side. NDC 49702-250-18	Adequate
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	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	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	N/A	N/A

reason why (e.g. to protect from light or moisture, to maintain stability, etc.)		
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	N/A
Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature.	Store at 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C and 30°C (59°F and 86°F) [See USP Controlled Room Temperature].	Adequate Storage condition is supported by stability data.
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	N/A
Include information about child-resistant packaging	child-resistant closure	Adequate

1.2.6 Other Sections of Labeling
None

1.2.7 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	Manufactured for: ViiV Healthcare Research Triangle Park, NC 27709 Manufactured by: GlaxoSmithKline Research Triangle Park, NC 27709	Adequate

2.0 PATIENT LABELING

The patient labeling comply with all regulatory requirements from a CMC perspective.

3.0 CARTON AND CONTAINER LABELING

3.1 Container Label

(b) (4)



3.2 Carton Labeling

(b) (4)



Item	Information Provided in the NDA	Assessor's Comments about Carton Labeling
Proprietary name, established name, and dosage form (font size and prominence)	Rukobia (fostemsavir) extended release tablets, 600 mg	Adequate The font of the Established name appears to be at least half as large as the letters comprising the proprietary name. Both propriety name and established name have the same font color and appear to have same prominence.
Dosage strength	600 mg	Adequate
Route of administration	Swallow tablets whole	Adequate
If the active ingredient is a salt, include the equivalency statement per FDA Guidance	Each film-coated tablet contains 600 mg of fostemsavir (equivalent to 725 mg fostemsavir tromethamine).	Adequate The applicant adopted FDA recommended strength expression based on active moiety first, followed by equivalency statement to the active ingredient salt.
Net contents (e.g. tablet count)	60 tablets	Adequate
"Rx only" displayed on the principal display	Yes	Adequate
NDC number	NDC 49702-250-18	Adequate
Lot number and expiration date	Yes (bottom of carton)	Adequate
Storage conditions. If applicable, include a space on the carton labeling for the user to write the new BUD.	Store at 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C and 30°C (59°F and 86°F) [See USP Controlled Room Temperature].	Adequate Consistent with PI and supported by stability data.
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use)	N/A	N/A
Other package terms include pharmacy bulk package and imaging bulk package which require "Not for direct infusion" statement.	N/A	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	

Item	Information Provided in the NDA	Assessor's Comments about Carton Labeling
Name of manufacturer/distributor	Manufactured for: ViiV Healthcare, RTP, NC 27709 Manufactured by: GlaxoSmithKline, RTP, NC 27709	Adequate
Medication Guide (if applicable)	N/A	N/A
No text on Ferrule and Cap overseal	None	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	N/A
And others, if space is available	N/A	N/A

Assessment of Carton and Container Labeling: {Adequate}

The container and carton labels, as of this review comply with all regulatory requirements from a CMC perspective

ITEMS FOR ADDITIONAL ASSESSMENT

None

Overall Assessment and Recommendation:

Adequate

Primary Labeling Assessor Name and Date: Hailin (Sheena) Wang, Ph.D. 05/11/2020

Secondary Assessor Name and Date: Stephen Miller, Ph.D. 05/26/2020



Sheena Hailin
Wang

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Stephen
Miller

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CHAPTER VI: BIOPHARMACEUTICS

NDA Number	212950; Type 1-NME; Breakthrough Therapy Designation - Granted
Assessment Cycle Number	1
Drug Product Name/ Strength	Rukobia™ (fostemsavir) Extended Release Tablet 600 mg
Route of Administration	Oral (600 mg orally twice daily with or without food)
Applicant Name	ViiV Healthcare
Therapeutic Classification/ OND Division	OND/OID/DAV
Associated INDs	IND 073916
Proposed Indication	Treatment of HIV infection
Primary Reviewer	Qi Zhang, Ph.D.
Secondary Reviewer	Elsbeth Chikhale, Ph.D.
Assessment Recommendation	Adequate

ASSESSMENT SUMMARY:

The Biopharmaceutics review was focused on: (1) evaluation of the adequacy of the proposed dissolution method and acceptance criteria, (2) Biopharmaceutics risk assessment, (3) bridging throughout product development, (4) in vitro alcohol dose-dumping, and (5) extended-release claim, for the proposed fostemsavir extended-release (ER) tablets. The overall summary for the Biopharmaceutics assessments is presented below.

1) Dissolution Method and Acceptance Criteria:

The Applicant's proposed dissolution specifications for batch release and stability testing, are based on the previously agreed upon dissolution "safe space" under IND 073916. The Applicant has revised the acceptance criterion for the 2 hours' time point to (b) (4)% from (b) (4)%, as per the FDA's recommendation during this review cycle.

Dissolution Method and Acceptance Criteria for Rukobia™ (fostemsavir) Extended Release Tablet, 600 mg				
Apparatus	Rotation Speed	Medium	Medium Volume/Temp	Acceptance Criteria
USP Apparatus 1 (Basket)	100 rpm	0.05 M phosphate buffer, pH 6.8	900 mL/37°C	2 hours: (b) (4)% 7 hours: (b) (4)% 24 hours: NLT (b) (4)%

2) Biopharmaceutics Risk Assessment:

The initial risk deemed dissolution as "High" from a Biopharmaceutics standpoint, since the proposed drug product is an extended release, high dose oral formulation utilizing

(b) (4) design. The risk can be mitigated with the implementation of the dissolution specification “safe space” for the proposed drug product.

3) Bridging Throughout Product Development:

The proposed commercial fostemsavir 600 mg ER tablets have the same formulation but a different manufacturing site than the ER tablet batches used in the Phase 3 studies. Bridging between the clinical and commercial drug products is deemed adequate based on the dissolution “safe space”, and f_2 comparisons in the three different pH dissolution media.

4) In Vitro Alcohol Dose Dumping:

The results of in vitro alcohol dose dumping testing indicate minimal influence of alcohol on the drug release, as less drug release from the proposed ER tablets with increasing amounts of alcohol but the difference in drug release profiles is insignificant (approximately <10% at each sampling time point and $f_2 > 50$) in 0.1 M HCl containing 0%, 5%, 20%, and 40% alcohol, and in pH 6.8 phosphate buffer containing 0%, 5%, 10%, and 20% alcohol. We defer to the OND and OCP review team for the recommendation with respect to risk assessment and labeling for concomitant use of alcohol.

5) Extended-Release Claim:

The proposed drug product meets the “Extended-Release” claim based on the totality of the data/information, according to the criteria cited in 21 CFR 325.25(f), mainly: (1) comparable pharmacokinetic steady-state performance between the proposed ER tablets and IR capsules, with established bioavailability profiles and ruling out the occurrence of dose-dumping; (2) extended-release characteristics in humans provides dosing benefit with respect to dosing frequency.

List of Submissions Being Assessed:

Document(s) Assessed	Date Received
Original Submission	09/24/2019
Response to Information Request	03/10/2020

Concise Description of Outstanding Issues (List bullet points with key information and update as needed):

None.

Recommendation:

From a Biopharmaceutics perspective, NDA 212950 for Rukobia™ (fostemsavir) Extended Release Tablets, 600 mg is recommended for **APPROVAL**.

B.1 BCS DESIGNATION

Assessment: *Not applicable to extended-release drug products.*

Solubility: The drug substance fostemsavir tromethamine (FTR) is a methyl phosphate prodrug of the active moiety temsavir (TMR). FTR was developed as a highly water-soluble prodrug of TMR. FTR has high aqueous solubility of (b) (4) mg/mL at pH (b) (4) and >250 mg/ mL from pH 3.7 to pH (b) (4) (Table 1). The active moiety, TMR, (b) (4) (b) (4) solubility of < (b) (4) mg/mL across the pH range (Table 2).

Permeability: FTR has been determined to have low Caco-2 permeability whereas TMR has high Caco-2 permeability. Following in vivo dissolution FTR is hydrolyzed to TMR by alkaline phosphatase in the gastrointestinal lumen, which is then rapidly absorbed due to its high membrane permeability. FTR was not quantifiable in most clinical samples, suggesting that FTR conversion to TMR is predominantly pre-systemic. The absolute bioavailability of TMR was 26.9%, per the proposed labelling.

Dissolution: The proposed FTR ER tablets contain (b) (4) (b) (4)

Table 1: pH Solubility Profile of Fostemsavir Tromethamine at 24°C

Solution pH	Solubility (mg/mL)
(b) (4)	(b) (4)
3.7	>250
(b) (4)	(b) (4)

Table 2: pH Solubility Profile of Temsavir

pH	Solubility (mg/mL)
(b) (4)	

B.2 DISSOLUTION METHOD AND ACCEPTANCE CRITERIA

Assessment: Adequate

The proposed dissolution method parameters, e.g., apparatus 1 (baskets) and agitation speed of 100 rpm, medium and pH ((b) (4) mL phosphate buffer, pH 6.8), were identified based on dissolution method development studies as summarized in the Validation of Analytical Procedure 3.2.P.5.3..

It is noted that the development and selection of the current dissolution method was previously provided [refer to IND 073916 Type C CMC EOP2 Meeting and meeting minutes 10/14/2015] and agreed with the FDA to construct the dissolution “safe space” within the conducted pivotal clinical batches [refer to IND 073916 meeting minutes 8/24/2017 and meeting preliminary comments 11/20/2017]

Dissolution Method [refer to IND 073916]

- ***Selection of Apparatus, Rotation Speed and Dissolution Medium***

Dissolution testing was performed

(b) (4)
(b) (4)

- ***Discriminating Capability of Dissolution Method***

The dissolution method showed the ability to discriminate release rates

(b) (4)

(b) (4)

(b) (4)

- **Validation of Dissolution Method**

An HPLC assay method (with UV detection at (b) (4) nm) is used to quantify the drug in the dissolution samples. The Applicant reported that the HPLC method was validated with regard to specificity, linearity, accuracy, precision, (b) (4) compatibility, solution stability, and robustness with respect to HPLC system changes and dissolution method parameter changes [e.g., rotation speed (\pm (b) (4) rpm), pH of dissolution media (\pm (b) (4)), and media buffer mM (\pm (b) (4))]. Refer to the Drug Product Review, for the evaluation of the adequacy of the analytical method validation (including the HPLC method used for dissolution testing).

Dissolution Acceptance Criteria

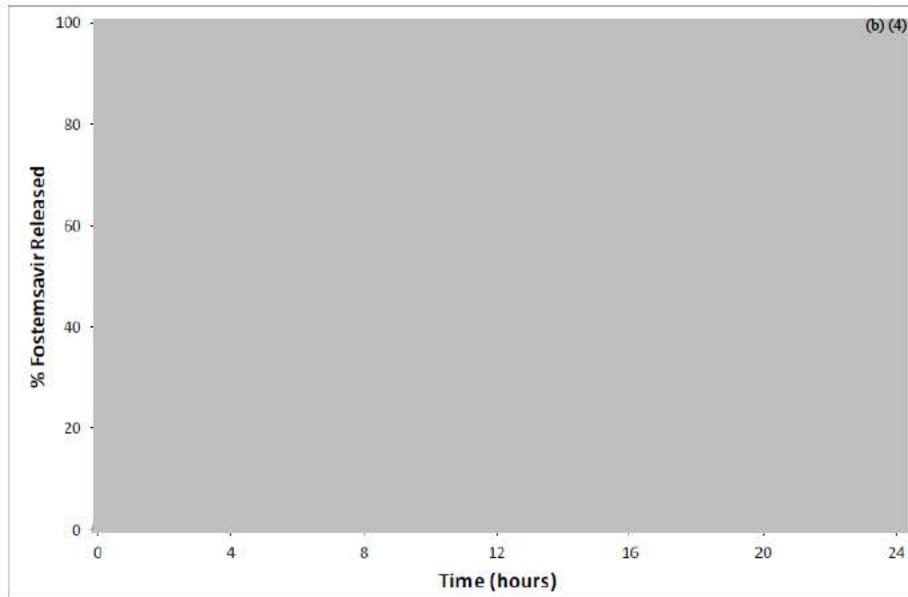
The Applicant has constructed a dissolution “safe space”, as described in Table 3 and Figure 5 (*i.e.*, a range from “lower bound based on knowledge” to “lower bound based on knowledge + (b) (4)%”); refer to section B.3). The knowledge space utilizes mean dissolution profiles from

- i) batch release data for 21 batches manufactured at (b) (4) BMS NJ used in the Phase 3 Study 205888 up to 96 weeks dosing (Table 4),
- ii) long-term stability data up to 36 months for the 3 clinical/primary stability batches manufactured at (b) (4) (as drug product up to 34 months old has been dosed in the Phase 3 Study 205888; Table 5), and
- iii) batches utilized in Study 206274 that were found to be bioequivalent between Phase 2b (b) (4) tablets and Phase 3 prototype (b) (4) tablets (Table 6).

Based on the constructed dissolution “safe space”, a three-point specification [\leq (b) (4)% in 2 hours”, “(b) (4)% in 7 hours”, and “ \geq (b) (4)% in 24 hours”] covering the initial, middle and final phases of the dissolution profiles, is proposed by the Applicant. The one-sided limit ((b) (4)%) for the initial 2-hour time point is not acceptable, and this Reviewer recommended (b) (4)% range at 2 hours for the proposed ER tablets (Information Request dated 2/28/2020). On 3/10/2020, the Applicant agreed to the FDA’s recommendation and revised the acceptance range for the 2 hours specification time point to (b) (4)%.

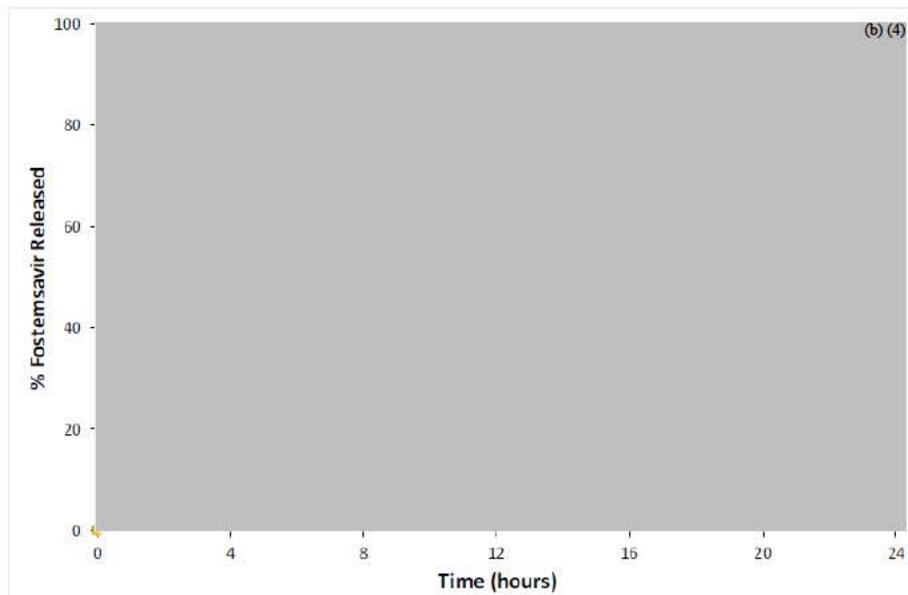
Noted that no significant change in dissolution for long-term stability data up to 36 months from the tablets manufactured at the clinical site, (b) (4) facility, and for accelerated and long-term stability data up to 6-month from the tablets manufactured at the commercial site (GSK, Parma, Italy). All results for dissolution complied with the specification.

Figure 1: Dissolution Profiles in (b) (4) M HCl and pH 6.8 Phosphate Buffer Using Baskets at Various Rotation Speeds



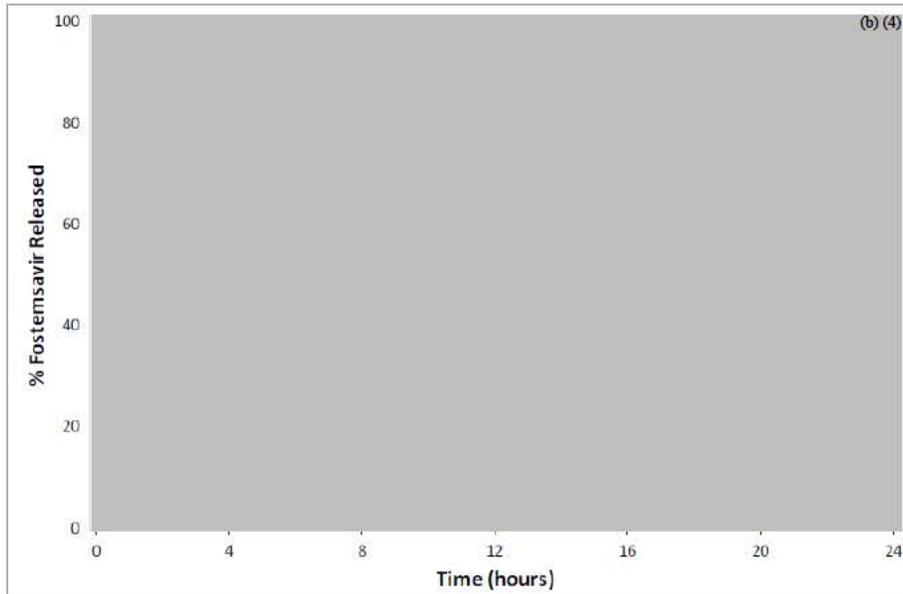
Note:
Error bars represent \pm one standard deviation.

Figure 2: Dissolution Profiles in pH 6.8 Phosphate Buffer Using Baskets and Paddles at Various Rotation Speeds



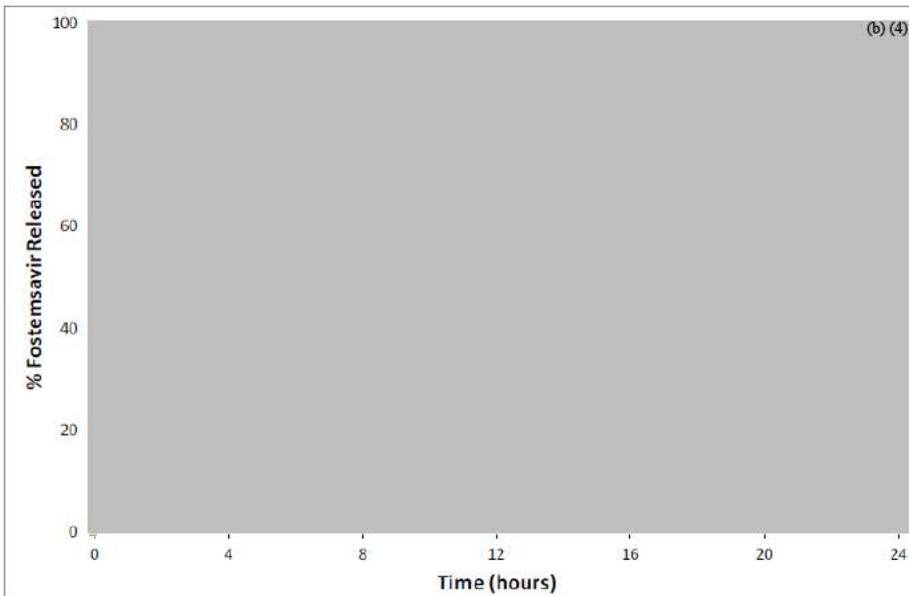
Note:
Error bars represent \pm one standard deviation.

Figure 3: Dissolution Profiles Formulations with \pm (b) (4) % (b) (4) Content



Note:
Error bars represent \pm one standard deviation.

Figure 4: Dissolution Profiles for Formulations (b) (4)



Note:
Error bars represent \pm one standard deviation.

Table 3: Dissolution Knowledge Space and Proposed Safe Space Bounds

	Time (hours)									
	1	2	3	5	7	10	14	18	24	
Knowledge Space Lower Bound (Release/Stability/BE)	(b) (4)									
Knowledge Space Upper Bound (Release/Stability/BE)										
Safe Space Lower Bound (Knowledge Space lower bound)										
Safe Space Upper Bound (Knowledge Space lower bound + ^(b) / ₍₄₎ %)										

Figure 5: Knowledge Space, Safe Space and Proposed Specification Limits

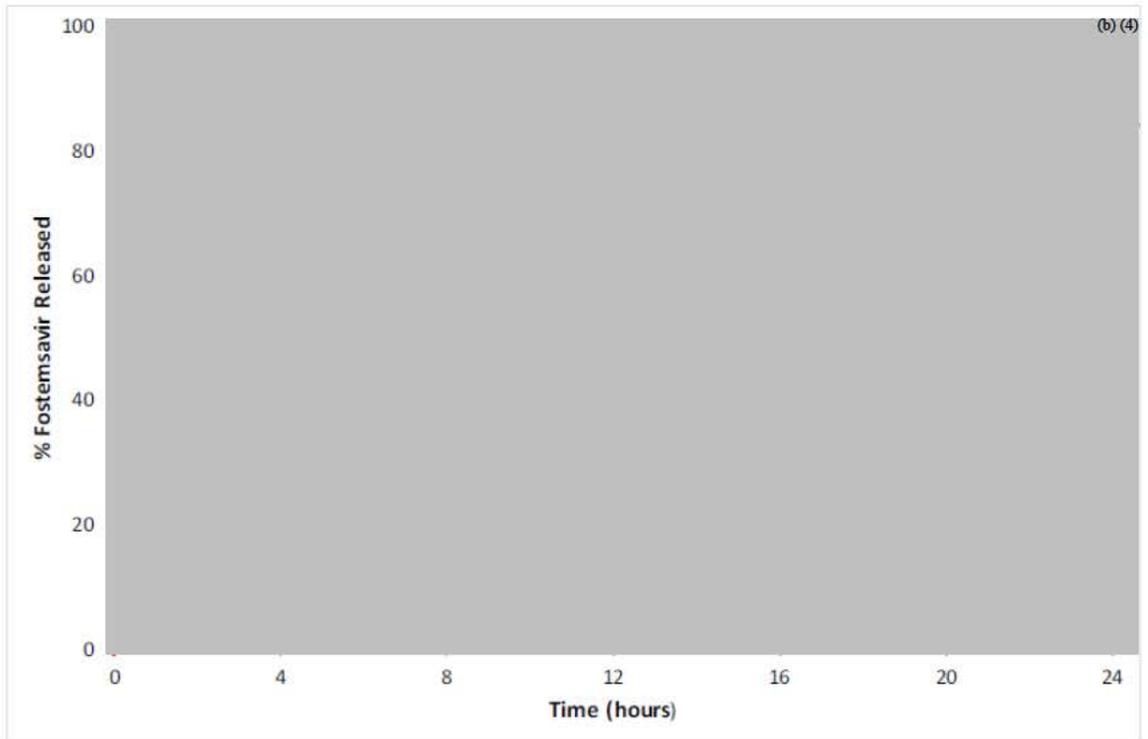


Table 4: Summary of Mean Dissolution Data at Release for 21 Phase 3 Batches
Manufactured at (b) (4) BMS NJ

	Time (hours)									
	1	2	3	5	7	10	14	18	24	(b) (4)
Minimum Mean % Released	(b) (4)									
Maximum Mean % Released										

Table 5: Summary of Mean Dissolution Stability Data after Storage for up to 36 Months
for Batches Manufactured (b) (4)

	Time (hours)									
	1	2	3	5	7	10	14	18	24	(b) (4)
Minimum Mean % Released	(b) (4)									
Maximum Mean % Released										

Table 6: Summary of Mean Dissolution Data at Release for Bioequivalent Phase 2b (b) (4)
(b) (4) and Phase 3 (b) (4) (Study 206274)

	Time (hours)									
	1	2	3	5	7	10	14	18	24	(b) (4)
Phase 2b (b) (4) Mean % Released	(b) (4)									
Prototype Phase 3 (b) (4) Mean % Released										

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

Assessment: *Adequate*

Dissolution “Safe Space”

The Applicant has had discussions with FDA regarding a potential IVIVC to support the drug product manufacturing site change under IND 073916 (refer to IND Type B meeting minutes 8/24/2017). The Applicant constructed (b) (4)

Ideally, robust and clinically relevant dissolution specifications (method and acceptance criteria) should be able to predict the in vivo performance (e.g. rank order relationship) in a range of release rates around the one characterizing the clinical batch (target). (b) (4)

(b) (4) FDA recommended, and agreed by the Applicant, that the dissolution “safe space” be defined as the “knowledge space lower bound” as the lower limits and the “knowledge space lower bound ” + (b) (4) % as the upper limits, and the knowledge space be based on the conducted pivotal clinical studies with generated in vitro dissolution for the target and variant drug product batches (refer to meeting preliminary comments 11/20/2017). FDA noted that the constructed dissolution “safe space” should be used for the setting of the dissolution acceptance criteria for QC. Wider dissolution acceptance criteria for QC (e.g., a range from “lower bound based on knowledge” to “lower bound based on knowledge + (b) (4) %”) will be acceptable, provided the upper bound is supported by data other than PK, such as safety data.

B.4 BRIDGING OF FORMULATIONS AND DRUG PRODUCT MANUFACTURING SITES

Assessment: *Adequate*

The product bridging among the formulations used during drug product development is illustrated in Figure 6. The initial formulation of FTR were immediate release (IR) capsules, 20 mg and 100 mg (b) (4)

The plasma levels were lower than clinical required, and therefore, an extended-release

tablet formulation

(b) (4) was developed.

(b) (4)

(b) (4)

Relative BA studies were conducted for IR capsules vs. uncoated ER tablets at a 600 mg total dose (Study 206261), and Phase 2b (b) (4) vs. Phase 3 (b) (4) (b) (4) film coated ER tablets, at a 1200 mg total dose (Study 206274). Dedicated relative BA study was not conducted between Phase 2a (b) (4) and Phase 2b (b) (4) 600 mg strength ER tablets. The Applicant demonstrated the similarity ($f_2 > 50$) via comparative in vitro dissolution profiles at pH (b) (4) and pH 6.8. In addition, the provided PK, efficacy and safety data support comparability between these two formulations; refer to the OCP and OND Reviews.

All initial Phase 3 clinical batches and primary stability batches were manufactured at (b) (4) and then at BMS, NJ. The GSK Parma facility is being used to maintain the continuity of supply for the ongoing Phase 3 study and is the proposed manufacturing site of the commercial drug product. The Applicant did not conduct a BE study to support the drug product manufacturing site change. Per agreement under IND 73916 meeting dated November 27, 2017, the constructed dissolution “safe space” (refer to B.3), along with f_2 comparisons in the three different pH dissolution media, be used to demonstrate equivalency between drug product manufactured at (b) (4) the commercial site, GSK Parma.

The current NDA submission provides dissolution profile data for three registration batches manufactured at the commercial site GSK Parma (batches 192414577, 192414580 and 192414583) showing that dissolution for all three batches are within the defined dissolution “safe space” at all sampling time points (Figure 7; complete dissolution data provided in 3.2.P.5.4 Batch Analysis). Additionally, dissolution experiments comparing these three registration batches and the Phase 3 drug products ((b) (4) batch AAE3698 and BMS batch AAM0609) have been performed using the proposed QC dissolution medium (pH 6.8) and in two other pHs (b) (4) (Figures 7-9). The results of the comparative dissolution testing, i.e., with essentially overlapping dissolution profiles and f_2 similarity values >75 , show that the manufacturing site change did not significantly alter the drug release rates for the registration batches made at the commercial site Parma, compared to the Phase 3 batches made at (b) (4) and BMS, thereby ensuring similar in-vivo performance of the drug product.

Figure 6: Schematic Diagram of Oral Formulations Used in Clinical Development and Formulation Bridging Strategy

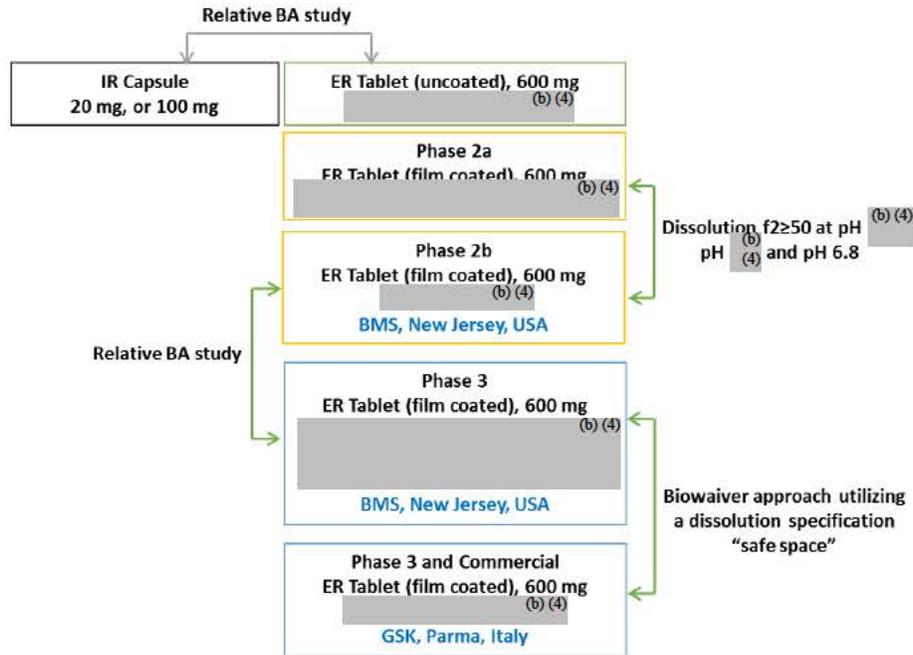


Figure 7: Comparison of Mean Dissolution Profiles of Phase 3 Batches and Registration Batches in pH 6.8 Buffer

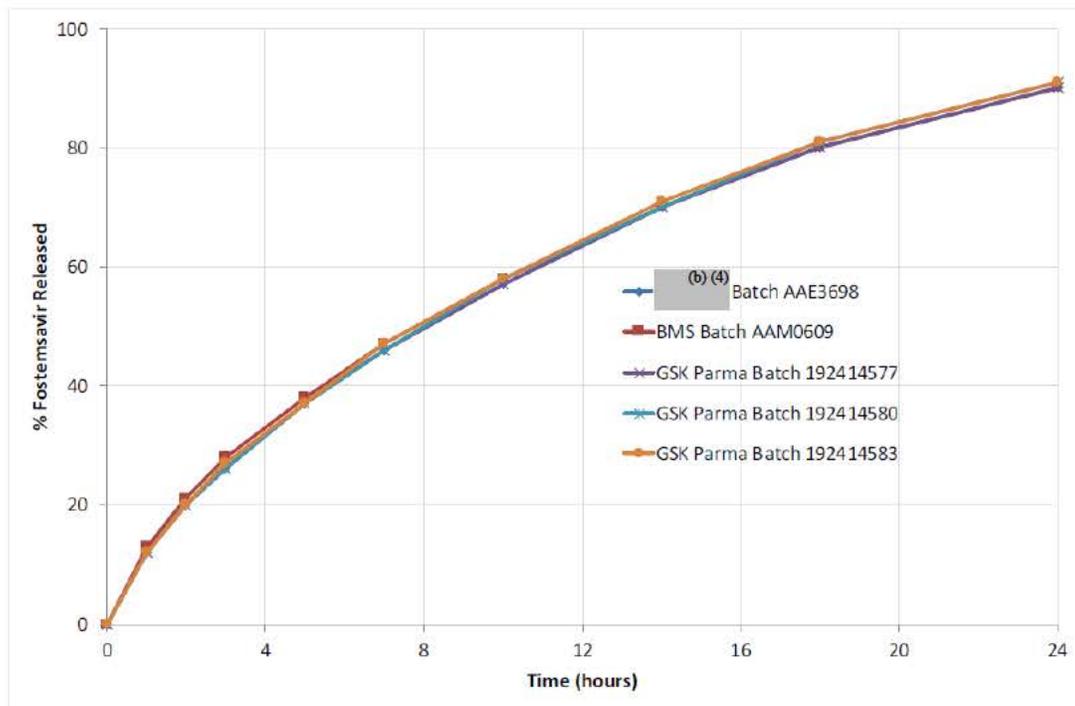


Figure 8: Comparison of Mean Dissolution Profiles of Phase 3 Batches and Registration Batches in pH (b) (4)

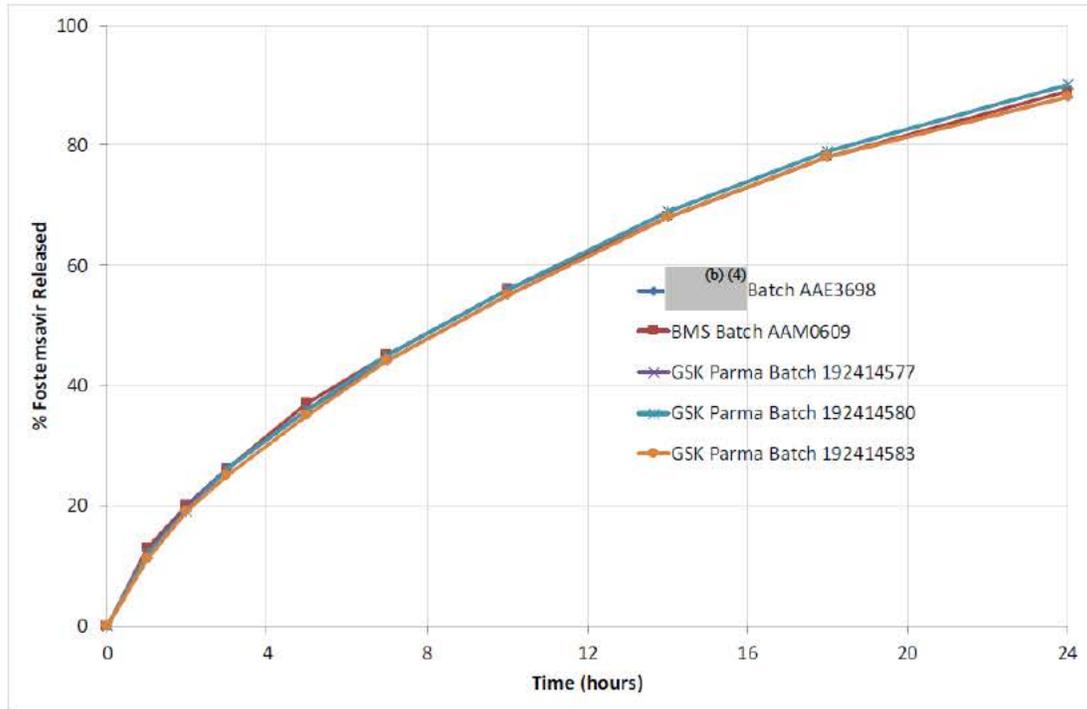
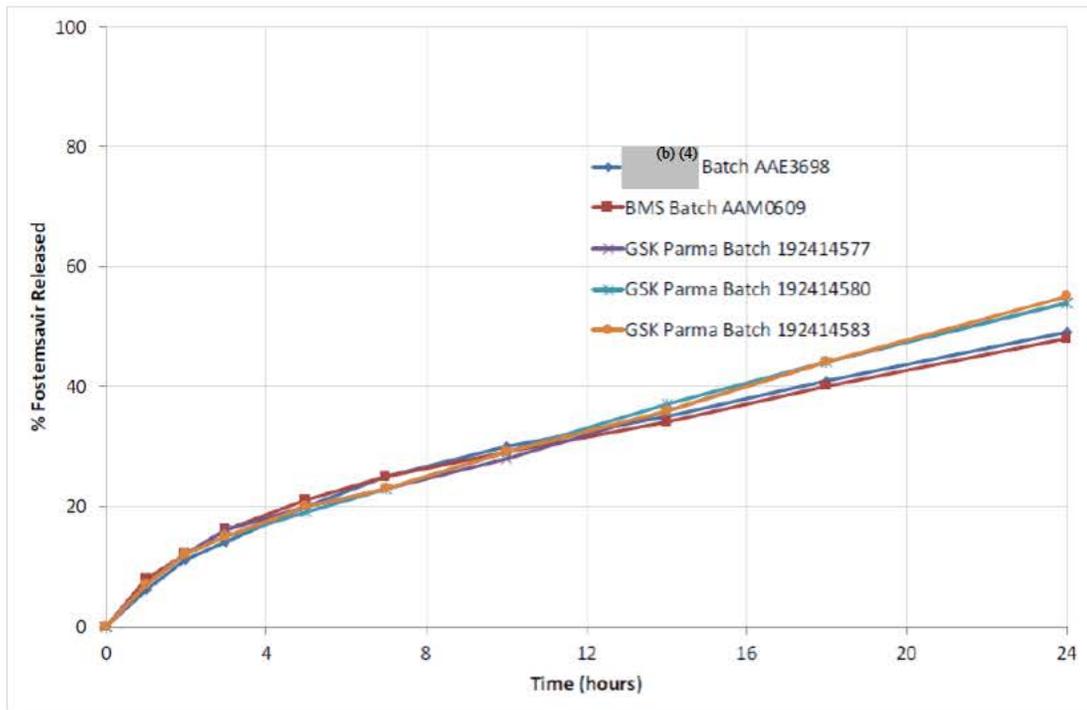


Figure 9: Comparison of Mean Dissolution Profiles of Phase 3 Batches and Registration Batches in (b) (4) M HCl pH (b) (4)



B.5 MODIFIED RELEASE ORAL DRUG PRODUCTS – *In-Vitro Alcohol Dose Dumping*

Assessment: Adequate

The Applicant conducted in vitro alcohol dose dumping studies in 0.1 M HCl containing 0%, 5%, 20%, and 40% ethanol, and in the proposed dissolution medium, pH 6.8 phosphate buffer, containing 0%, 5%, 10%, and 20% ethanol, using the proposed dissolution method conditions [USP Apparatus 1 (Baskets) at 100 RPM with (b) (4) mL medium]. The results of in vitro alcohol dose dumping testing show less drug release with increasing amounts of alcohol (Figures 10 and 11); however, the differences in drug release profiles at pH 6.8 are insignificant (approximately <10% at each sampling time points and $f_2 > 50$) compared to the reference (0% alcohol dissolution profile); all the tablets tested in 0.1 M HCl had approximately <10% drug release in 2 hours with different concentrations of alcohol. Overall, the results indicate minimal influence of alcohol on the drug release, considering the similar dissolution profiles at pH 1.2 and pH 6.8 with up to 40% or 20% alcohol, respectively. However, we defer to the OND and OCP review team for the recommendation with respect to risk assessment and labeling regarding concomitant use of alcohol.

Figure 10: Comparison of Mean Dissolution Profiles Generated in (b) (4) ML 0.1 M HCl with Various Alcohol Concentrations Using the Proposed Dissolution Method Conditions [USP Apparatus 1 (Baskets) At 100 RPM]

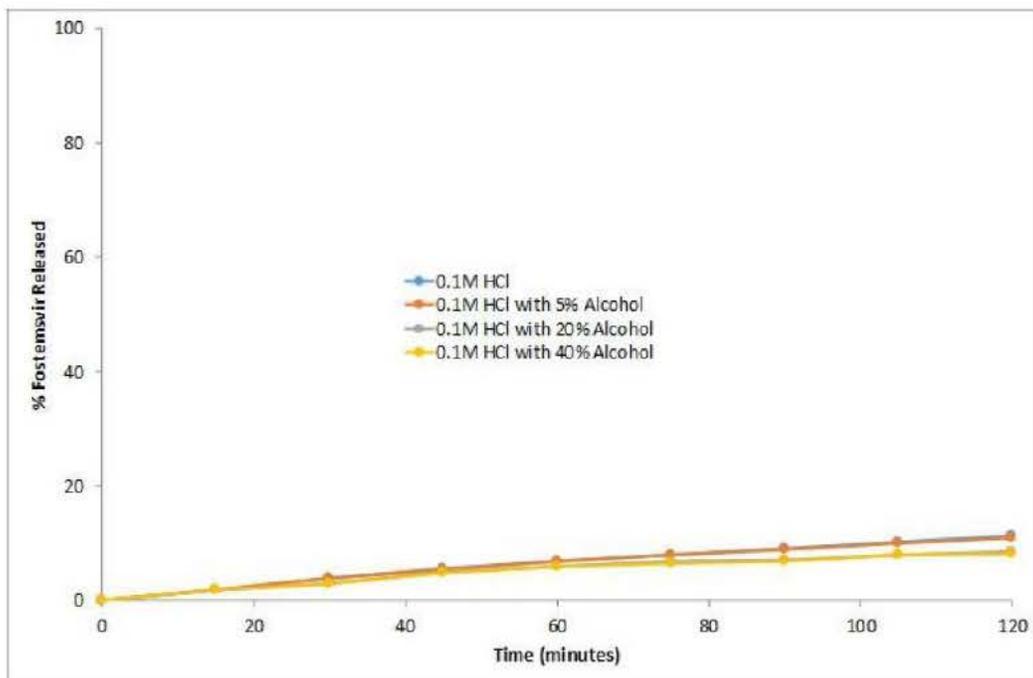
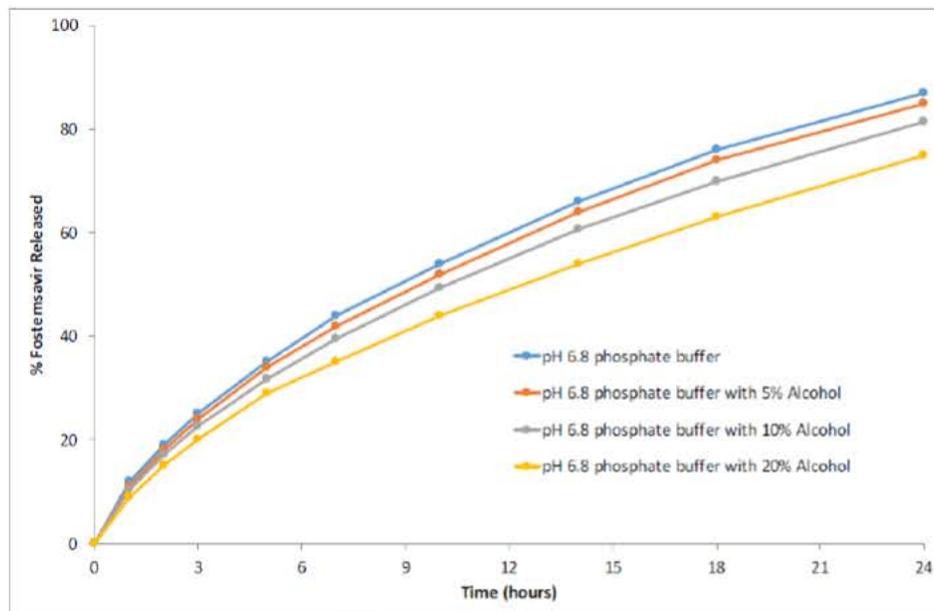


Figure 11: Comparison of Mean Dissolution Profiles Generated in (b) (4) mL pH 6.8 Phosphate Buffer with Various Alcohol Concentrations Using the Proposed Dissolution Method Conditions [USP Apparatus 1 (Baskets) At 100 RPM]



B.6 EXTENDED RELEASE DOSAGE FORMS –Extended Release Claim

Assessment: Adequate

Collectively, the following information support the extended release claim for the proposed drug product, according to the criteria cited in 21 CFR 325.25(f): (1) The proposed formulation exhibits the extended release characteristics without dose-dumping under various pH conditions in vitro. The drug substance is formulated with

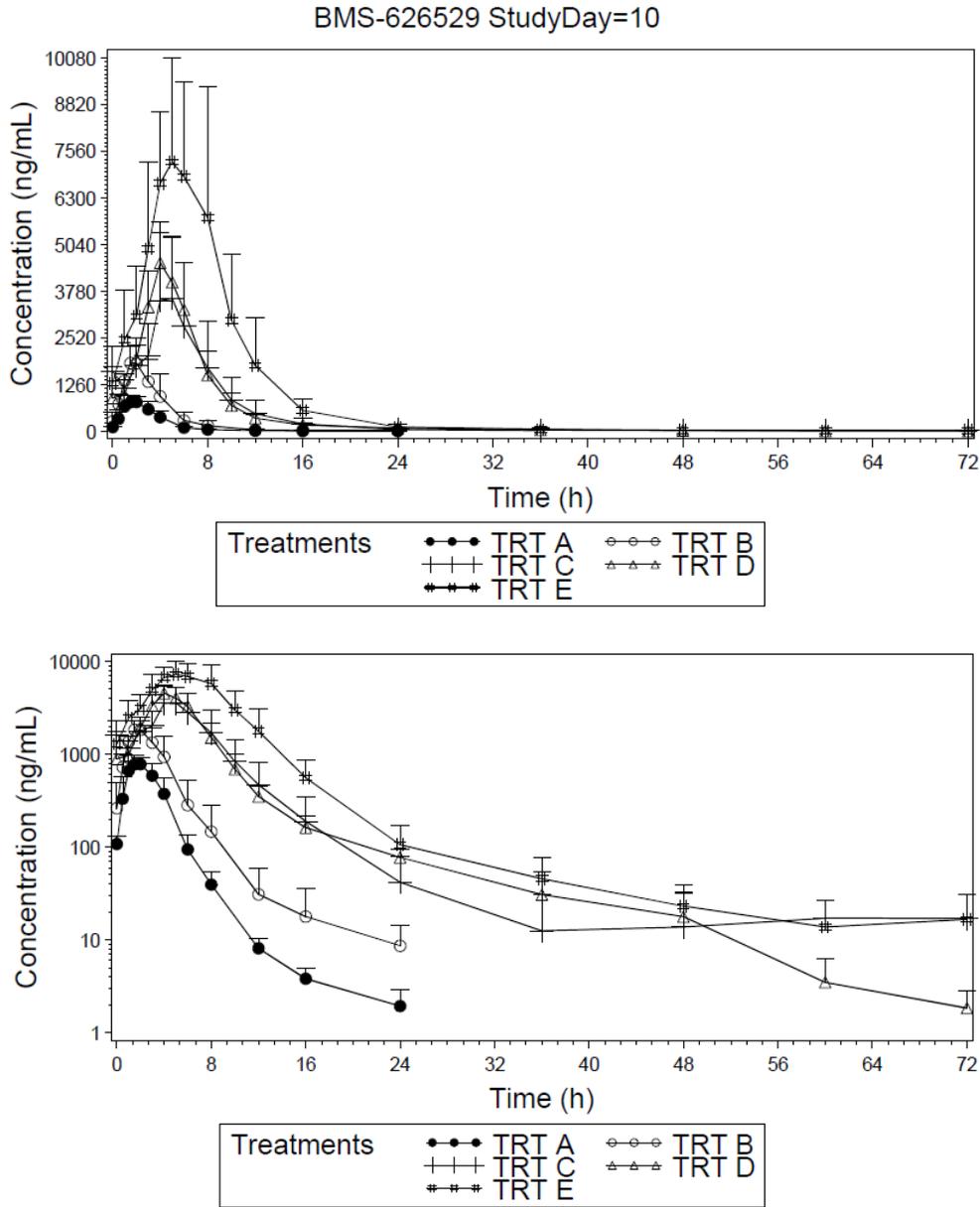
(b) (4)

(b) (4) As shown in

the in vitro dissolution studies, less than (b) (4)% of FTR is released during the first 2 hours, approximately (b) (4)%, and (b) (4) at 7 hours and 24 hours in the dissolution medium from pH (b) (4) to pH 6.8, mimicking the slow FTR release of the tablet and prolonged availability of the active moiety TMR for absorption in the intestinal tract.

(2) Comparable pharmacokinetic steady-state parameters/performance between the proposed ER tablets and IR capsules, and extended-release characteristics in humans to provide dosing benefit with respect to dosing frequency (Study 206262). FTR ER tablets administered over the strength dose range of 600 to 1200 mg Q12h were associated with a longer Tmax (4-5 h vs 1.5-2 h) and t1/2 (7-14 h vs 3.2-4.5 h) compared with FTR IR capsules administered over the strength dose range of 100 to 200 mg Q8h. CLT/F ranged from 422 to 484 ml/min for IR capsules, 681 ml/min for ER tablets. Figure 12; also refer to OCP review.

Figure 12: Mean plasma concentration-time profiles of FTR (BMS-626529) - Treatments A - E (Day 10) - Linear Scale and Log Scale



Abbreviations: IR, immediate release; ER, extended release; Q8h, every 8h; Q12, every 12 h; RTV: ritonavir
 Treatment A (100 mg IR Q8h)
 Treatment B (200 mg IR Q8h)
 Treatment C (600 mg ER+RTV Q12h)
 Treatment D (1200 mg ER)
 Treatment E (1200 mg ER+RTV Q12h)



Qi
Zhang

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