CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

212904Orig1s000

PRODUCT QUALITY REVIEW(S)

U.S. FOOD & DRUG ADMINISTRATION

RECOMMENDATION

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

NDA 212904
Assessment #1

Drug Product Name	Fotivda tivozanib
Dosage Form	Capsules
Strength	0.89 and 1.34 mg
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	Aveo Pharmaceuticals, Inc.
US agent, if applicable	N/A

Submission(s) Assessed	Document Date	Discipline(s) Affected
Original 0001	3/31/2020	All: DS, DP, OPMA, Biopharm
SND 0008	6/4/2020	All
SND 0014	7/13/2020	All
SND 0021	8/24/2020	All
SND 0023	9/30/2020	All

QUALITY ASSESSMENT TEAM

Discipline	Primary Assessment	Secondary Assessment
Drug Substance	Rajan Pragani	Ali Al Hakim
Drug Product	Rohit Tiwari	Anamitro Banerjee
Manufacturing	Diane Goll	Bogdan Kurtyka
Microbiology	N/A	
Biopharmaceutics	Qi Zhang	Banu Zolnik
Regulatory Business Process Manager	Kristine Leahy	
Application Technical Lead	Xiao Hong Chen	
Laboratory (OTR)	N/A	
Environmental	Rohit Tiwari	Scott Furness

QUALITY ASSESSMENT DATA SHEET

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Assessment Completed	Comments
[redacted] (b) (4)	III	[redacted]	(b) (4)	Adequate	11/30/2020	No DMF review is necessary since adequate information in the NDA.
	III			Adequate	11/30/2020	No DMF review is necessary since adequate information in the NDA.
	III			Adequate	11/30/2020	No DMF review is necessary since adequate information in the NDA.
	III			Adequate	11/30/2020	No DMF review is necessary since adequate information in the NDA.
	III			Adequate	11/30/2020	No DMF review is necessary since adequate information in the NDA.
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	III			Adequate	11/30/2020	No DMF review is necessary since adequate information in the NDA.
	III			Adequate	11/30/2020	No DMF review is necessary since adequate information in the NDA.
	III			Adequate	11/30/2020	No DMF review is necessary since adequate information in the NDA.

(b) (4)	III	(b) (4)	Adequate	11/30/2020	No DMF review is necessary since adequate information in the NDA.

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

Document	Application Number	Description
Submission and review documents	IND 75547	Original IND submitted to Division of Oncology Products 1 for the potential treatment of solid tumors in cancer patients on 5/30/2007.

2. CONSULTS
N/A

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

EXECUTIVE SUMMARY

IQA NDA Assessment Guide Reference

I. RECOMMENDATIONS AND CONCLUSION ON APPROVABILITY

The product quality review team recommends Approval of NDA 212904 based on the adequate CMC information submitted in the NDA and acceptable status for all manufacturing facilities. The following comment should be included in the action letter if the NDA is approved:

A 60-month expiry dating period is granted for Fotiva (b) (4) stored at: 20° to 25°C (68° to 77°F); excursions permitted to 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature].

II. SUMMARY OF QUALITY ASSESSMENTS

A. Product Overview

The applicant submits a 505b1 NDA for immediate release (IR) Tivozanib (b) (4) Tivozanib is a quinoline urea derivative. It is a potent and selective inhibitor of vascular endothelial growth factor (VEGF) receptors and is developed for the treatment of advanced renal cell carcinoma. The drug product is an immediate release, solid oral, hard gelatin capsule filled with (b) (4) drug substance (tivozanib hydrochloride) and excipients (mannitol and magnesium stearate). The recommended dose of tivozanib is one 1.34 mg oral capsule taken once daily, with or without food, on a 28-day schedule consisting of 21 days of treatment followed by 7 days off treatment. The drug substance is the monohydrate form of the hydrochloride salt of tivozanib. To support the approval of the NDA, the applicant conducted an active comparator-controlled Phase 3 study (tivozanib vs. sorafenib) in subjects with relapsed or refractory advanced renal cell carcinoma. The drug substance is manufactured (b) (4) The drug product is an immediate release, solid oral, hard gelatin capsule filled with (b) (4) drug substance (tivozanib hydrochloride monohydrate) and excipients (mannitol and magnesium stearate). The drug product is manufactured in two strengths containing 1.0 mg and 1.5 mg tivozanib hydrochloride, equivalent to 0.89 mg and 1.34 mg of tivozanib (free base), respectively. The drug load is very low and is different for the two strengths, 0.89 mg and 1.34 mg tivozanib, being 1.25% and 1.875%, respectively. A 60-month expiry was granted for the drug stored at 20-25°C.

Proposed Indication(s) including Intended Patient Population	FOTIVDA is a kinase inhibitor indicated for the treatment of adult patients with relapsed or refractory advanced renal cell carcinoma (RCC) following two or more prior systemic therapies.

Duration of Treatment	Until disease progression
Maximum Daily Dose	• Recommended Dose: 1.34 mg once daily with or without food for 21 days on treatment followed by 7 days off treatment (28-day cycle) until disease progression or unacceptable toxicity. • Dose interruptions and/or dose reduction may be needed to manage adverse reactions. • For patients with moderate hepatic impairment, reduce the dose to 0.89 mg for 21 days on treatment followed by 7 days off treatment (28-day cycle).
Alternative Methods of Administration	N/A.

B. Quality Assessment Overview

Drug Substance: Adequate

The drug substance tivozanib is a hydrochloride salt that is produced as a hydrate. The CMC information submitted demonstrates quality control for the manufacture of the drug substance.

The drug substance structure has been adequately characterized. The polymorph (b) (4), salt identity, water content, particle size distribution is controlled in the drug substance specification. Two specified impurities (b) (4) with limits above the ICH Q3A qualification threshold were forwarded to the nonclinical reviewer. It was concluded that both limits are adequately qualified. Although (b) (4) is Ames positive, the nonclinical reviewer stated that the indication falls under the category of advanced cancer, and thus, the limit and control strategy for (b) (4) is acceptable. Elemental impurities are not included in the drug substance specification with adequate justification and residual solvents are controlled with acceptable ICH limits. The manufacturing has been sufficiently described and appears reasonable. The starting materials (b) (4) are at reasonable points in the synthesis and comply with ICH Q11. Based on the stability data provided for the registration batches, a proposed retest period of (b) (4) months ((b) (4) % RH) is acceptable for tivozanib hydrochloride.

Drug Product: Adequate

The tivozanib hydrochloride drug product is an immediate release, solid oral, hard gelatin capsule that is filled with (b) (4) excipients and tivozanib hydrochloride drug substance. The drug product is manufactured in two strengths: 0.89 mg and 1.34 mg tivozanib (equivalent to 1.0 mg and 1.5 mg tivozanib hydrochloride, respectively). (b) (4) The levels of the mannitol and magnesium stearate in the proposed drug product formulations are below the maximum daily exposure as per the

IID database for the oral administration. The clinical trial formulation is the same as the proposed marketing formulation. No excipient sourcing from human/animal origin is used in the proposed drug products. (b) (4) The applicant has demonstrated that the drug product manufacturing process does not affect any change in the polymorphic form, (b) (4) of the drug substance. The provided batch analyses data demonstrate that the applicant is able to reproduce the quality of the drug product as per the specification. No out of specification results were observed in any of the tests for the batch analyses. Both strengths (0.89 mg and 1.34 mg) of tivozanib drug product will be packed in a high-density polyethylene bottle with a (b) (4) cap. The bottle will be packed into a cardboard outer carton with an accompanying patient information leaflet. Based on the provided stability data for the tivozanib hydrochloride drug products, all samples met the acceptance criteria at the end of the study. No out of specifications results were observed in any of the data points. The data does not show any changes to any of the tested parameters during the stability study period. The applicant proposed a shelf life of 60 months based on the available long term and accelerated stability data for 0.89 mg and 1.34 mg tivozanib drug products in their respective container closure system. This proposed expiration dating period is acceptable and may be granted.

Labeling: Adequate

The container carton labels and the labeling for the Prescribing Information are deemed acceptable after the applicant revised the labeling based on FDA's comments.

Manufacturing: Adequate

The commercial drug product manufacturing facility (Catalent in Kansas City, MO) *was* referred to District. Subsequently, District recommended approval and OPMA concurred and approved.

(b) (4) will be shipped from the DP manufacturing facility in Kansas City, MO (Catalent) to a primary packaging facility (b) (4) that is approvable per file review.

The commercial drug substance manufacturing facility (b) (4) was referred to District. Subsequently, District recommended approval and OPMA concurred and approved.

The proposed commercial manufacturing process is (b) (4)

Manufacturing steps include (b) (4) [redacted] The manufacturing process information in the NDA is deemed acceptable.

Biopharmaceutics: Adequate

The Applicant's proposed dissolution method [USP Apparatus 2 (paddle) at 50 rpm, 900 mL of 1 mM HCl with 0.5% w/v SDS, 37°C; "Q = (b) (4) % at 20 min"] was previously deemed adequate under NDA 204408. In the current submission, the Applicant provided additional data to confirm that the proposed dissolution method is optimal, which is deemed acceptable.

The proposed commercial Tivozanib Capsules, 0.89 mg and 1.34 mg have the same formulation and manufacturing site as the batches used in the pivotal Phase 3 study. There are differences in manufacturing site between the batches used in the supportive clinical studies and commercial batches. Bridging between the clinical and commercial drug products was deemed adequate under NDA 204408 based on the dissolution profiles comparisons in the three different pH dissolution media.

The initial risk deemed dissolution as "Moderate" from a Biopharmaceutics standpoint, because the drug substance has low solubility. The Applicant has included the controls of drug substance (b) (4) [redacted]. Additionally, the Tmax (10 hours) of Tivozanib is not considered critical regarding treatment effect or disease control for the proposed indication. The risk is further mitigated with the implementation of the dissolution specification for the proposed drug product.

Microbiology (if applicable): Choose an item.

N/A

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 Evaluation**	**Lifecycle Considerations/ Comments****
Assay, Stability	• Formulation • Container closure • Raw materials • Process parameters • Scale/equipments • Site	L	(b) (4)	Acceptable	The assay shows no discernable change on DP stability for up to 60 month. Total degradation products showed no trending for up to 60 month on DP stability.
Physical stability (solid state)	• Formulation • Raw materials • Process parameters • Scale/equipments • Site	M		Acceptable	Crystallinity is monitored in the DS stability study. Up to 60 months DS stability data showed no change.
Content uniformity	• Formulation • Container closure • Raw materials • Process parameters • Scale/equipments • Site	H		Acceptable	DP manufacturing process studies showed content uniformity is in control.
Microbial limits	• Formulation • Container closure • Process parameters • Scale/equipments • Site	L		Acceptable	Microbial limit test result conform to specifications up to 60 month on stability.
Dissolution – BCS Class II & IV	• Formulation • Container closure • Raw materials • Process parameters • Scale/equipments • Site	M		Acceptable	60-month dissolution data on stability showed no trend or significant changes.

D. List of Deficiencies for Complete Response

None.

Application Technical Lead Name and Date:

Xiao Hong Chen
February 16, 2021

Xiao Chen

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U.S. FOOD & DRUG ADMINISTRATION

CHAPTER I: DRUG SUBSTANCE

Drug Substance Name	Tivozanib hydrochloride
NDA Number	212904
Assessment Cycle Number	
DMF Number	n/a
DMF Status	Choose an item.
Applicant Name	Aveo Pharmaceuticals Inc.
DMF Holder	n/a

Assessment Recommendation: **Adequate**

Assessment Summary:
The drug substance tivozanib is a hydrochloride salt that is produced as a hydrate. The CMC information submitted demonstrates quality control for the manufacture of the drug substance.

The drug substance structure has been adequately characterized. The polymorph (b) (4), salt identity, water content, particle size distribution is controlled in the drug substance specification.

Two specified impurities (b) (4) with limits above the ICH Q3A qualification threshold were forwarded to the nonclinical reviewer. It was concluded that both limits are adequately qualified. Although (b) (4) is Ames positive, the nonclinical reviewer stated that the indication falls under the category of advanced cancer, and thus, the limit and control strategy for (b) (4) is acceptable. Element impurities are not included in the drug substance specification with adequate justification and residual solvents are controlled with acceptable ICH limits. The manufacturing has been sufficiently described and appears reasonable. The starting materials (b) (4) are at reasonable points in the synthesis and comply with ICH Q11.

Based on the stability data provided for the registration batches, a proposed retest period of (b) (4) months ((b) (4)% RH) is acceptable for tivozanib hydrochloride.

List Submissions being assessed (*Table*):

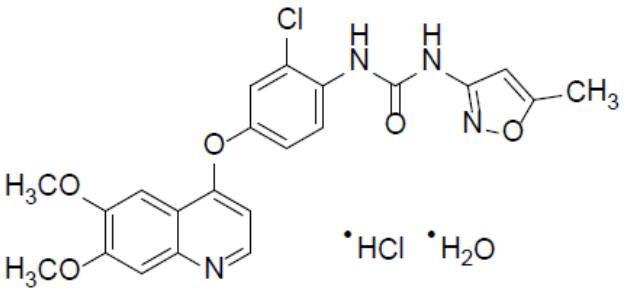
Document(s) Assessed	Date Received
Original CMC Submission	03/31/2020
Quality Amendment	08/24/2020

Highlight Key Issues from Last Cycle and Their Resolution: not applicable

Concise Description of Outstanding Issues (*List bullet points with key information and update as needed*): not applicable

S.1 GENERAL INFORMATION

Summary of the Information



Property	Summary Data
Description	White to light brown powder
Solubility[1,2]	dimethyl sulfoxide: > 100 mg/mL (freely soluble) methanol: 4.32 mg/mL (slightly soluble) ethanol: 8.70 mg/mL (slightly soluble) water: 0.09 mg/mL (practically insoluble) octanol: 96 µg/mL (very slightly soluble) pH 1 1.17 µg/mL (practically insoluble) pH 4 3.89 µ/mL (practically insoluble) pH 7 2.92 µ/mL (practically insoluble) pH 10 0.273 µ/mL (practically insoluble) pH 12 0.887 µ/mL (practically insoluble)
Melting range[3]	181 – 193°C (followed by decomposition)
pKa	5.9
Hygroscopicity	The drug substance is not hygroscopic.
Polymorphism	(b) (4)
Chirality	There are no chiral centers in the molecule.
Crystallinity	Photomicroscopy indicates that drug substance (b) (4)
Thermal Properties	Differential scanning calorimetry (DSC) analysis shows a broad endothermic peak at approximately 130°C that correlates with loss of water or solvent, an endothermic onset at approximately 181°C that indicates the start of melting and an endothermic peak at approximately 190 °C indicative of melting. Thermogravimetric analysis (TGA) showed a 3.6% decrease in weight up to 150°C which is consistent with the theoretical value for water for the monohydrate form of the drug substance.
Partition coefficient (Log P) (octanol:water)[4]	4.09 (at 40°C)

Assessment: *Adequate.* The description is sufficient for a complex organic compound. The drug substance is tivozanib hydrochloride. It shows low solubility, has no chiral centers, (b) (4)

S.2 MANUFACTURE

Commercial Synthetic Scheme and Process Flow Diagram

(b) (4)

Assessment: *Adequate.* The manufacturing has been sufficiently described and appears reasonable. The starting materials are suitably placed in the synthesis.

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R REGIONAL INFORMATION

Comparability Protocols

Assessment: *n/a*

Post-Approval Commitments

Assessment: *n/a*

Lifecycle Management Considerations

n/a

DRUG SUBSTANCE LIST OF DEFICIENCIES

n/a

Primary Drug Substance Assessor Name and Date:

Rajan Pragani, Ph.D., 11/20/20

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

Ali Al-Hakim, Ph.D., 11/20/20

Rajan
Pragani

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Date: 12/04/2020 11:33:40AM
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Ali
Al Hakim

Digitally signed by Ali Al Hakim
Date: 12/04/2020 11:51:20AM
GUID: 508da71e00029dfb374f4f37edac02c6

DRUG PRODUCT

Product Background: Tivozanib hydrochloride is an inhibitor of all three vascular endothelial growth factor (VEGF) receptors. This application seeks approval for the treatment of patients with refractory renal cell carcinoma. The recommended dose of tivozanib is one 1.34 mg (equivalent to 1.5 mg tivozanib hydrochloride capsule) once daily with or without food for 21 days on treatment followed by 7 days off treatment. The tivozanib hydrochloride drug product is an immediate release, solid oral, hard gelatin capsule that is filled with (b) (4) excipients and tivozanib hydrochloride drug substance. The drug product is manufactured in two strengths: 0.89 mg and 1.34 mg tivozanib (equivalent to 1.0 mg and 1.5 mg tivozanib hydrochloride).

NDA: 212904

Drug Product Name / Strength: FOTIVDA/ 0.89 mg and 1.34 mg

Route of Administration: Oral administration

Applicant Name: Aveo Pharmaceuticals

Review Summary: The tivozanib hydrochloride drug product is an immediate release, solid oral, hard gelatin capsule that is filled with (b) (4) excipients and tivozanib hydrochloride drug substance. The drug product is manufactured in two strengths: 0.89 mg and 1.34 mg tivozanib (equivalent to 1.0 mg and 1.5 mg tivozanib hydrochloride). (b) (4) The levels of the mannitol and magnesium stearate in the proposed drug product formulations are below the maximum daily exposure as per the IID database for the oral administration. The clinical trial formulation was same as the proposed formulation. No excipient sourcing from human/animal origin is used in the proposed drug products. (b) (4) The provided batch analyses data demonstrate that the applicant is able to reproduce the quality of the drug product as per the specification. No out of specification results were observed in any of the tests for the batch analyses. Both strengths (0.89 mg and 1.34 mg) of tivozanib (equivalent to 1.0 mg and 1.5 mg of tivozanib hydrochloride) drug product will be packed in a high-density polyethylene bottle with a (b) (4) cap. The bottle will be packed into a cardboard outer carton with an accompanying patient information leaflet. Based on the provided stability data for the tivozanib hydrochloride drug products, all samples met the

acceptance criteria at the end of the study. No out of specifications results were observed in any of the data points. The data does not show any changes to any of the tested parameters during the stability study period. The applicant proposed a shelf life of 60 months based on the available long term and accelerated stability data for 0.89 mg and 1.34 mg tivozanib drug products in their respective container closure system. This proposed expiration dating period is acceptable and may be granted.

List Submissions being reviewed (table): SN001, SN0008

Highlight Key Outstanding Issues from Last Cycle: None

Concise Description Outstanding Issues Remaining: *None*

P.1 Description and Composition

The tivozanib hydrochloride drug product is an immediate release, solid oral, hard gelatin capsule that is filled with (b) (4) *excipients and tivozanib hydrochloride drug substance. The drug product is manufactured in two strengths: 0.89 mg and 1.34 mg tivozanib (equivalent to 1.0 mg and 1.5 mg tivozanib hydrochloride). A size "4" hard gelatin capsule is used for both strengths. The 0.89 mg strength consists of a dark blue opaque cap and bright yellow opaque body, imprinted in yellow ink with "TIVZ" on the cap and in dark blue ink with "LD" on the body. The 1.34 mg strength consists of a bright yellow opaque cap and a bright yellow opaque body, imprinted in dark blue ink with "TIVZ" on the cap and in dark blue ink with "SD" on the body.*

Component/composition table

Table 1: Composition of the Tivozanib Hydrochloride 0.89 mg and 1.34 mg Capsules

Component	Quality Standard[1]	Function	Amount per Capsule			
			0.89 mg[2]		1.34 mg[3]	
			mg	%	mg	%
Tivozanib hydrochloride monohydrate[4]	In-house, Section 3.2.S.4.1	Active Pharmaceutical Ingredient	1.0	1.250	1.5	1.875
Mannitol[4]	USP	(b) (4)				
Magnesium stearate	NF					
		Total weight	80.0	100.0	80.0	100.0
Capsule, hard gelatin, Size 4[5]	In-house, Section 3.2.P.4.1	Capsule shell	1		1	
Capsule Imprint Ink(s)[6]	N/A	N/A	trace amount		trace amount	

1 USP-NF: USP = United States Pharmacopeia; NF = National Formulary
2 Each capsule contains 0.89 mg tivozanib . equivalent to 1.0 mg tivozanib hydrochloride.
3 Each capsule contains 1.34 mg tivozanib ,equivalent to 1.5 mg tivozanib hydrochloride.
4 (b) (4)
5 Information on the components of the hard gelatin capsules is provided in Table 2 (0.89 mg) and Table 3 (1.34 mg).
6 Information for the components of the imprint inks is provided in Table 4 and Table 5.

- The composition of empty hard gelatin capsules for 0.89 mg and 1.34 mg tivozanib hydrochloride drug product are tabulated below.

Table 2: Composition of the 0.89 mg Capsule Shell

Component	Quality Standard[1]	Function	Composition	
			Cap	Body
FD&C Blue #2	21CFR	(b) (4)		
FDA Yellow Iron Oxide	21CFR; USP/NF			
Titanium dioxide	21CFR; USP/NF			
Gelatin	USP/NF			

[1] USP-NF: USP = United States Pharmacopeia; NF = National Formulary; CFR = United States Code of Federal Regulations.

Table 3: Composition of the 1.34 mg Capsule Shell

Component	Quality Standard[1]	Function	Composition	
			Cap	Body
FDA Yellow Iron Oxide	21CFR; USP/NF	(b) (4)		
Titanium dioxide	21CFR; USP/NF			
Gelatin	USP/NF			

[1] USP-NF: USP = United States Pharmacopeia; NF = National Formulary; CFR = United States Code of Federal Regulations.

- The compositions of the ink used for imprinting are tabulated below.

(b) (4)

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P.8 Stability

- The stability studies were conducted on three lots of tivozanib hydrochloride drug products of each strength (0.89 mg and 1.34 mg) as per ICHQ1A(R2). The stability data were generated on the drug products packaged in 21-count 30 cc HDPE bottles with induction sealed and child resistant closures. The proposed long term storage condition is 25±2°C/60±5% RH and the data for the accelerated condition of 40±2°C/75±5% RH is also provided.
- Tivozanib hydrochloride 0.89 mg strength capsule drug product in the proposed container closure system (Lots # L0305316, L0305358, L0305360). 1) The stability time points for the long term conditions were 0, 1, 3, 6, 9, 12, 18, 24, 36, 48 and 60 month and data was reported for all of them. No out of specification results reported. No trends are apparent. No changes to assay, degradation products or dissolution. 2) The data for 6 months under the accelerated conditions show that the drug product is stable and no change in any of the tested parameters was noted. A slight upward trend in the amount of degradation product was noted but its amount was still within the proposed specification.
- Tivozanib hydrochloride 1.34 mg strength capsule drug product in the proposed container closure system (Lots # L0305318, L0305363, L0305365). The stability time points for the long term conditions were 0, 1, 3, 6, 9, 12, 18, 24, 36, 48 and 60 month and data was reported for all of them. No out of specification results reported. No trends are apparent. No changes to assay, degradation products or dissolution. 2) The data for 6 months under the accelerated conditions show that the drug product is stable and no change in any of the tested parameters was noted. A slight upward trend in the amount of degradation product was noted but its amount was still within the proposed specification.
- (b) (4)
- Temperature excursion study : Thermal stability study was conducted to support temperature excursions that may occur during shipment or storage of the drug product. These conditions included three cycles of storage conditions between -20°C (freezing) and 50°C (thawing). Under these conditions, no new degradation products were reported or no out of specification limits were reported for description, assay, dissolution test limits or degradation products.
- A photostability study was conducted with 0.89 mg and 1.34 mg strength tivozanib hydrochloride drug product as per ICH Q1B guidance option 2. Analyses included changes

to description, assay, degradation products, water and dissolution for one lot of 0.89 mg (Lot L0305360) and 1.34 mg (Lot L0305365) tivozanib capsule drug products. The tivozanib hydrochloride drug product exhibited good chemical and physical stability upon direct exposure to light. The exposed drug product showed no degradation compared to the dark control. No trends are apparent. No changes to assay, purity, or dissolution was noted. Therefore, the applicant's conclusion that further light exposure testing in the packaging configuration is not required is reasonable based on ICH Q1B guideline.

Reviewer's Assessment: Adequate.

Based on the provided stability data for the tivozanib hydrochloride drug products, all samples met the acceptance criteria at the end of the study. No out of specifications results were observed in any of the data points. There was no change in any of the tested parameters during the stability study period. In the temperature excursion studies, the drug products maintain their integrity as per the proposed specification. The forced degradation studies indicate that the analytical method for the determination of impurity is stability indicating.

The applicant proposed the **shelf life of 60 months** based on the available long term and accelerated stability data for 0.89 mg and 1.34 mg tivozanib drug products in their respective container closure system. This proposed expiration dating period is acceptable and may be granted. The applicant's additional stability data supports their conclusion that drug product does not need to protected from light.

Post-Approval Stability Protocol and Commitment

One lot of the drug product of each strength will be placed for the stability studies annually for each year in which at least one lot of that strength is produced. The post-approval stability protocol includes the following tests and timepoints.

Table 1: Post Approval Stability Protocol

Test	Timepoint (Month)[1]							
	0[2]	6	12	18	24	36	48	60
Description	X	X	X	X	X	X	X	X
Assay by HPLC	X	X	X	X	X	X	X	X
Impurities by HPLC	X	X	X	X	X	X	X	X
Dissolution	X	X	X	X	X	X	X	X

[1] X = Testing is conducted

[2] Release testing results may be used for time zero.

Reviewer's Assessment: The proposal for the post approval stability tests and time points are adequate.

R Regional Information

Environmental Analysis

Reviewer's Assessment: The applicant has submitted a claim of categorical exclusion including a statement of no extraordinary circumstances. The categorical exclusion cited at 21 CFR 25.31(b) is appropriate for the estimated amount of drug to be produced for direct use in the U.S. The claim of categorical exclusion is acceptable.

Methods Verification Package

Reviewer's Assessment: NA.

Comparability Protocols

Reviewer's Assessment:

Post-Approval Commitments

Reviewer's Assessment:

Lifecycle Management Considerations

Reviewer's Assessment:

Primary Drug Product Reviewer Name and Date: Rohit V. Tiwari, Ph.D., November 30, 2020.

Secondary Reviewer Name and Date: Anamitro Banerjee, Ph.D., November 30, 2020

Rohit Tiwari

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Anamitro Banerjee

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MANUFACTURING INTEGRATED ASSESSMENT

Application ID	NDA 212904
Drug Product Name	tivozanib
Strengths	1.0 and 1.5 mg
Dosage Form	Capsule
Administration Route	Oral
Indication	Treatment of patients with relapsed or refractory renal cell carcinoma (RCC)
Applicant Name	Aveo Pharmaceuticals, Inc.

Changes to last review are in blue text

I. Manufacturing Summary

Facility Assessment Recommendation: Adequate

Process Assessment Recommendation: Adequate

Assessment Summary:

The commercial drug product manufacturing facility (Catalent in Kansas City, MO) was referred to District. Subsequently, District recommended approval and OPMA concurred and approved.

(b) (4) will be shipped from the DP manufacturing facility in Kansas City, MO (Catalent) to a primary packaging facility (b) (4) that is approvable per file review.

The commercial drug substance manufacturing facility (b) (4) was referred to District. Subsequently, District recommended approval and OPMA concurred and approved.

The proposed commercial manufacturing process (b) (4)

List Submissions being assessed (Table):

Document Description (SD #)	Date Received
0001 () Original Submission	03/31/2020
0008 (8) Response to CMC IR	06/04/2020
0014 (14) Response to Process IR	07/13/2020
0023 (23) Response to Process IR	09/30/2020

Highlight Key Issues from Last Cycle and Their Resolution:

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

Third round: None

Second round:
Applicant requested to:

- (b) (4)

First round:
Applicant requested to:

(b) (4)

1. *Post-Approval Commitments and Lifecycle Management Considerations*

Postmarketing commitments (PMC)?	No
Post-approval inspection?	No
Lifecycle considerations	No

Panorama link

2. *Facilities Table*

Facility name and address	FEI	Responsibilities and profile code(s)	Status

	(b) (6)	Drug substance: manufacture, release and stability testing, primary packaging || 356h Status: Active CSN	Approve - Based on Previous History
SSCI, A Division of AMRI (formerly Aptuit Scientific Operations, LLC) 3065 Kent Avenue, West Lafayette, IN, USA, 47906-1076	3001452090	Drug substance: XRPD testing. || 356h Status: Active LCP	Approve - Based on Previous History
Catalent CTS, Inc. 10245 Hickman Mills Drive, Kansas City, MO, USA, 64137	3002929455	Drug product: manufacturing of capsules, QC release testing, stability storage testing, and bulk packaging. || 356h Status: Active CHG	Approve - Based on Previous History
	(b) (4)	Drug product: primary packaging and labeling || 356h Status: Active (b) (4) CHG	Approve - Based on Previous History

II. Drug Product Manufacturing

(b) (4)

21 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

(b) (4)

[redacted]

V. List of Outstanding Information Request/Deficiencies:

Outstanding Deficiencies Collation Table

VI. Signature Block

Round#	Primary Name	Secondary & Other Names	Date of Completion	Assessment Outcome	Facility OMIR
1	Diane Goll	Bogdan Kurtyka	6/22/2020	IR	Approve
1	Diane Goll	Bogdan Kurtyka	9/10/2020	IR	Approve
2	Diane Goll	Bogdan Kurtyka	10/30/2020	Adequate	Approve

Diane Goll

Digitally signed by Diane Goll
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Bogdan Kurtyka

Digitally signed by Bogdan Kurtyka
Date: 11/05/2020 01:24:25PM
GUID: 502d1ab500002af17f12c233c16bf8b1

CHAPTER VI: BIOPHARMACEUTICS

NDA Number	212904; 505 b (1)-NME
Assessment Cycle Number	1
Drug Product Name/ Strength	FOTIVDA™ (tivozanib) Capsules 0.89 mg and 1.34 mg (equivalent to 1.0 mg and 1.5 mg tivozanib hydrochloride)
Route of Administration	Oral (1.34 mg taken orally once daily with or without food for 21 days on treatment followed by 7 days off treatment)
Applicant Name	AVEO Pharmaceuticals, Inc.
Therapeutic Classification/ OND Division	Oncology OND/OOD/DO2
Associated INDs	IND 075547
Proposed Indication	For the treatment of adult patients with relapsed or refractory advanced renal cell carcinoma (RCC) following two or more prior systemic therapies.
Primary Reviewer	Qi Zhang, Ph.D.
Secondary Reviewer	Banu Zolnik, Ph.D.
Assessment Recommendation	***Adequate***

ASSESSMENT SUMMARY:

The Applicant, AVEO Pharmaceuticals, is seeking approval of the proposed FOTIVDA™ (tivozanib) Capsules, 0.89 mg and 1.34 mg for the treatment of adult patients with relapsed or refractory advanced renal cell carcinoma (RCC). Tivozanib is an inhibitor of all three Vascular Endothelial Growth Factor (VEGF) receptors (VEGFR-1, 2, and 3). The proposed tivozanib product is an immediate release, solid oral, hard gelatin capsule that is filled with (b) (4) excipients and tivozanib hydrochloride drug substance. The clinical program in support of this NDA includes a pivotal Phase 3 Study (AV-951-15-303), and three supportive clinical studies (submitted under NDA 204408[1] for the proposed tivozanib capsule): a Phase 3 Study (AV-951-09-301), an Extension Study (AV-951-09-902) and a Phase 2 Study (TGR-1202-101).

The Biopharmaceutics review is focused on evaluation of (i) the adequacy of the proposed dissolution method and acceptance criterion, (ii) bridging throughout the drug product development, and (iii) risk assessment.

1) Dissolution Method and Acceptance Criterion

The Applicant's proposed dissolution method was previously deemed adequate under NDA 204408[2]. In the current submission, the Applicant provided additional data to

[1] FDA issued a complete response letter on June 6, 2013. AVEO withdrew NDA 204408 on June 17, 2013.
[2] Biopharmaceutics Reviews by Dr. John Duan, dated 5/8/2013 in DARRTS

confirm that the proposed dissolution method is optimal. Based on the totality of the information and data provided (complete dissolution with acceptable variability at 20 minutes, method's discriminating ability and robustness, and relevant Biopharmaceutics considerations [control of API particle size, and Tmax is not critical]), the proposed dissolution method and acceptance criterion of Q = (b) (4)% at 20 minutes, for the drug product batch release and stability testing are acceptable.

Approved Dissolution Method and Acceptance Criterion for FOTIVDA™ (tivozanib) Capsules, 0.89 mg and 1.34 mg				
Apparatus	**Speed**	**Medium**	**Temp**	**Acceptance Criterion**
USP Apparatus 2 (Paddle) with sinkers	50 rpm	Tier 1: 900 mL of 1 mM HCl with 0.5% w/v SDS Tier 2: 750 mL of 1 mM HCl with with 750,000 units/L pepsin for 10 minutes, and then add 150 mL of 1 mM HCl with 3% w/v SDS	37°C	Q= (b) (4)% in 20 minutes

2) Bridging Throughout Product Development

The proposed commercial Tivozanib Capsules, 0.89 mg and 1.34 mg have the same formulation and manufacturing site as the batches used in the pivotal Phase 3 study. There are differences in manufacturing site between the batches used in the supportive clinical studies and commercial batches. Bridging between the clinical and commercial drug products was deemed adequate under NDA 204408 based on the dissolution profiles comparisons in the three different pH dissolution media.

3) Biopharmaceutics Risk Assessment

The initial risk deemed dissolution as "Moderate" from a Biopharmaceutics standpoint, because the drug substance has low solubility. The Applicant has included the controls of drug substance (b) (4). Additionally, the Tmax (10 hours) of Tivozanib is not considered critical regarding treatment effect or disease control for the proposed indication. The risk is further mitigated with the implementation of the dissolution specification for the proposed drug product.

List Submissions Being Assessed:

Document(s) Assessed	Date Received
Original Submission	03/31/2020
Response to Information Request	06/04/2020

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

None.

RECOMMENDATION:

From a Biopharmaceutics perspective, NDA 212904 for FOTIVDA™ (tivozanib) Capsules, 0.89 mg and 1.34 mg is recommended for APPROVAL.

B.1 BCS DESIGNATION

Assessment: *A BCS designation is not requested nor required.*

Tivozanib hydrochloride drug substance is produced [redacted] and used in clinical supplies and registration stability batches. The Applicant claimed that tivozanib hydrochloride drug substance is a BCS Class 4 drug with low solubility and low permeability because tivozanib hydrochloride exhibits low solubility irrespective of pH and low permeability based on a Caco-2 cell study.

Solubility: The solubility data are consistent with the indicated BCS class of the drug substance, as the solubility is approximately 1-4 µg/mL over the physiological pH range from pH 1 to pH 7. The concentration of the highest strength of 1.5 mg in 250 mL is 6 µg/mL which is above the solubility limit over the physiological pH range, therefore, this drug substance is considered low solubility.

Permeability: In the Caco-2 cell model, [^{14}C]-Tivozanib showed low apparent permeability and was not a substrate or inhibitor of P-glycoprotein (P-gp) at clinically relevant concentrations (Study 8231062 of Nonclinical Summaries 2.6.4.). Note that the absolute bioavailability and relative bioavailability of tivozanib have not been determined. According to the labeling, unchanged tivozanib constituted 90% of the radioactive drug components in serum following a single radiolabeled 1.34 mg dose of tivozanib to healthy subjects.

Dissolution: The proposed tivozanib capsule is manufactured [redacted] with excipients, mannitol and magnesium stearate, and filling [redacted] in size 4 hard gelatin capsule. The tivozanib capsule dissolves in 20 minutes using the proposed dissolution method.

B.2 DISSOLUTION METHOD AND ACCEPTANCE CRITERION

Assessment: ***Adequate***

Dissolution Method Development: The method development, i.e. the justification for the selection of the apparatus and rotation speed (Apparatus 2 at 50 rpm), dissolution medium (900 mL 1 mM HCl), and the type and level of added surfactant (0.5% SDS) in the dissolution medium, were previously deemed to be adequate under NDA 204408. Briefly, due to the aqueous solubility limitation, surfactant is needed in the dissolution medium to achieve sink conditions and complete dissolution for tivozanib hydrochloride.

[redacted]

(b) (4)

Applicant provided additional data to support that the proposed dissolution method is appropriate for the proposed tivozanib capsule.

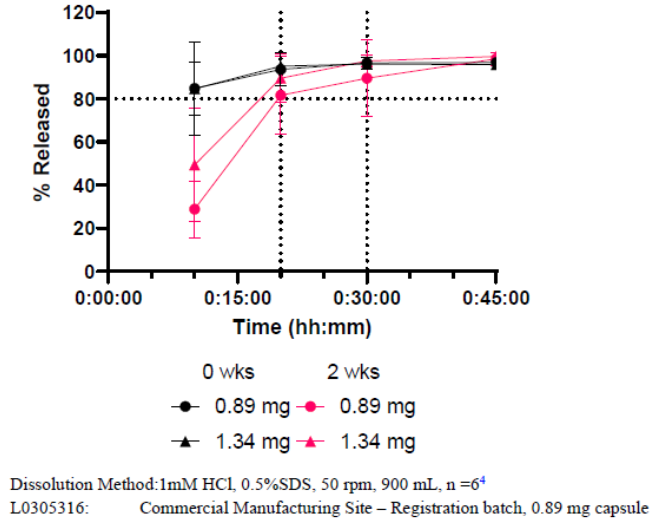
Surfactant Level

(b) (4)

Discriminating Ability of Dissolution Method

The proposed dissolution method was shown stability indicating. The dissolution data presented in **Figure 2** show significant change in dissolution when the proposed tivozanib capsules were exposed to accelerated open dish conditions (40 °C/75% RH) for 2 weeks. The observed dissolution suppression is possibly due to the crosslinking of the gelatin in the capsule shells.

Figure 2: Dissolution Comparison of of Tivozanib Capsules Stored at 40 °C/75% RH in Open Dish for 0 and 2 Weeks



Source: Figure 6 in 3.2.P.2.2 Drug Product

The Applicant also showed that the method discriminated dissolution rates with respect to changes in process parameters (b) (4) Although the average dissolution passed the proposed specification of Q (b) (4)% at 20-minute, the dissolution of runs 3, 4, 6, 9 and 12 was less than (b) (4)% at 20 minutes in 1 mM HCl/0.5% SLS medium thus failing Stage I dissolution.

Tier 2 Dissolution Method: The dissolution method proposed involves two-tier dissolution testing; the dissolution medium for Tier 1 testing is 1 mM HCl with 0.5% SDS, while the medium for Tier 2 testing is 1 mM HCl with 0.5% SDS containing pepsin at 750,000 units per 900 mL. The Tier-2 test is conducted in sequential order, i.e., pepsin digests the cross-linked capsule shells in the first stage of the experiment, while SDS, a substance known to inhibit the action of the enzyme, is added in the second stage in order to obtain suitable dissolution profiles by improving drug wettability. Note that Tier 2 testing is performed only when required, i.e. the product fails in dissolution test in the Tier 1 test, due to cross-linking of gelatin capsules when stored at accelerated conditions. The proposed two-tier dissolution method approach is in line with the USP Dissolution Chapter <711> and is acceptable.

Dissolution Acceptance Criterion: During the review cycle of the previous NDA submission, the Applicant was recommended to tight the dissolution acceptance criterion from [redacted]. In the current submission, a dissolution acceptance criterion of Q=[redacted]% at 20 minutes is proposed by the Applicant based on: (1) the communication with the FDA in 2013 regarding the dissolution results of the process robustness study (refer to **Figure 3**), (2) an evaluation of the disintegration specification for the capsule shell (NMT [redacted]min), and (3) the dissolution profiles from batch release data and long-term stability data up to 60 months for the registration/stability and validation batches. The Applicant noted that the individual dissolution values at 20 minutes are in the range of [redacted]%, for the batch release and long-term stability test, respectively. The dissolution profile data for the registration, validation and launch batches are provided in Section 3.2.P.5.6.12 and the mean release dissolution data for the launch batches are illustrated in **Figure 4** and **Figure 5** for the 0.89 mg and 1.34 mg capsule batches, respectively.

From a Biopharmaceutics perspective, the Applicant's proposal of dissolution acceptance limit, Q=[redacted]% in 20 minutes instead of [redacted]minutes, is acceptable, by taking into consideration the following: (1) Complete dissolution with acceptable variability at 20

minutes for registration and stability batches at batch release and stability testing. (2) The proposed drug product formulation is (b) (4) 3) Critical material attributes (CMAs) that could impact the solubility/dissolution are (b) (4) (4) Tmax of tivozanib is 10 hours with a range from 3 to 24 hours, additionally, the Tmax is not critical because the drug product will be administered (1.34 mg taken orally once daily with or without food for 21 days on treatment followed by 7 days off treatment) to adult patients with relapsed or refractory advanced RCC. (5) (b) (4) .

Figure 4: Launch Batches Release Dissolution Profile Plots – 0.89 mg Capsules

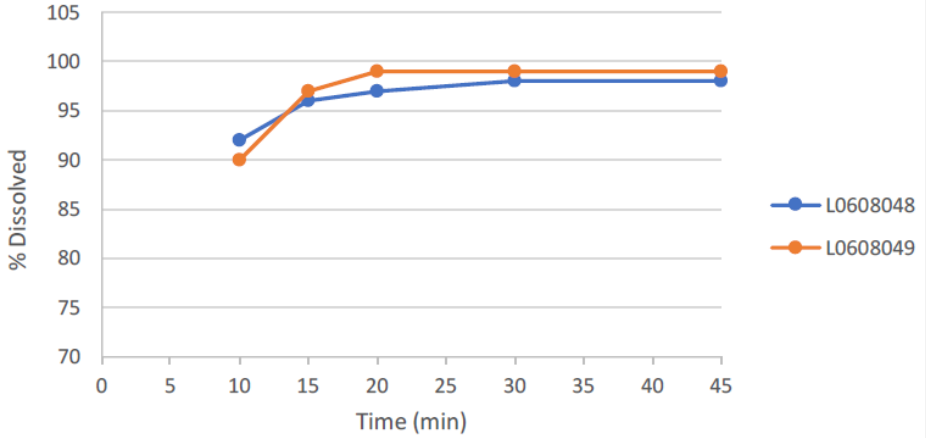
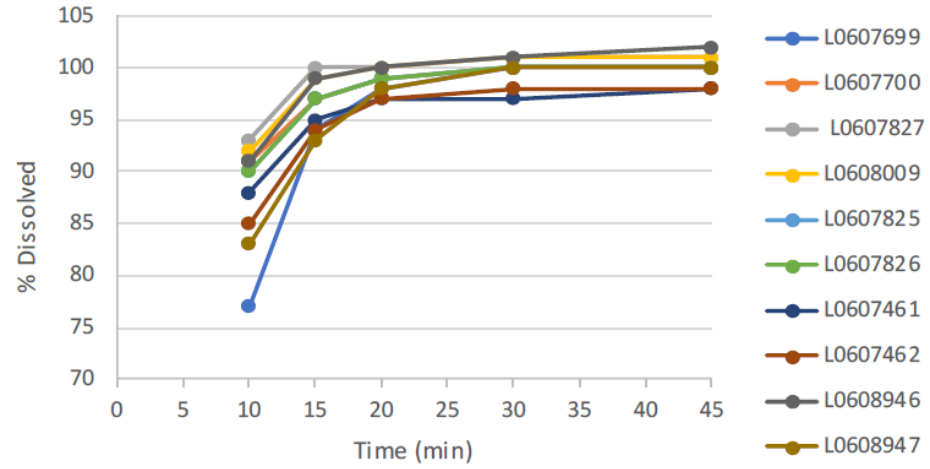


Figure 5: Launch Batches Release Dissolution Profile Plots – 1.34 mg Capsules



Source: Figure 1 and Figure 2 of 3.2.P.5.6 Justification of Specifications

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

Assessment: *Not reported in the current submission.*

B.12 BRIDGING OF FORMULATIONS

Assessment: ***Adequate***

A capsule formulation of tivozanib has been used throughout the entire clinical development program. (b) (4)

A list of all the capsule batches manufactured for clinical trials, registration/stability, process validation, and commercial/stability is presented in Table 1 of 3.2.P.5.4. There are differences in capsule color and manufacturing site between the batches used in the clinical studies and commercial batches. Bridging between the clinical and commercial tivozanib capsules was deemed adequate under NDA 204408 based on the dissolution profiles comparisons in the three different pH dissolution media, using a model-independent multivariate confidence region procedure (refer to Biopharmaceutics Review[1] by Dr. John Duan, dated 5/8/2013 in DARRTS). The formulation composition of the commercial batches is the same as the most recent 2 clinical batches used in the pivotal Phase 3 Study AV-951-15-303. Therefore, no additional information is needed to bridge the drug product formulations in the current submission.

Qi Zhang

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Banu Zolnik

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Date: 12/04/2020 04:42:43PM
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LABELING

{For NDA Only}

I. Package Insert

1. *Highlights of Prescribing Information*

Item	Information Provided in NDA
Product Title (Labeling Review Tool and 21 CFR 201.57(a)(2))	
Proprietary name and established name	Provided
Dosage form, route of administration	Provided
Controlled drug substance symbol (if applicable)	NA
Dosage Forms and Strengths (Labeling Review Tool and 21 CFR 201.57(a)(8))	
Summary of the dosage form and strength	Provided

2. *Section 2 Dosage and Administration*

Item	Information Provided in NDA
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(12))	
Special instructions for product preparation (e.g., reconstitution, mixing with food, diluting with compatible diluents)	NA

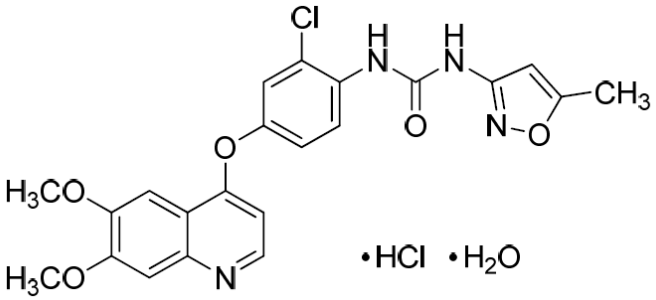
3. *Section 3 Dosage Forms and Strengths*

- 1.34 mg Capsule – Hard gelatin capsule with a bright yellow opaque cap imprinted with "TIVZ" in dark blue ink and a bright yellow opaque body imprinted with "SD" in dark blue ink.
- 0.89 mg Capsule – Hard gelatin capsule with a dark blue opaque cap imprinted with "TIVZ" in yellow ink and a bright yellow opaque body with "LD" in dark blue ink.

Item	Information Provided in NDA
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(4))	
Available dosage forms	Provided
Strengths: in metric system	Provided
Active moiety expression of strength with equivalence statement (if applicable)	Strength expressed based on active moiety, consistent with the USP salt policy. Equivalency statement provided in Section 11.
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.	Provided

4. *Section 11 Description*

- Tivozanib hydrochloride is a tyrosine kinase inhibitor (TKI). Tivozanib hydrochloride has the chemical name 1-{2-chloro-4-[(6,7-dimethoxyquinolin-4-yl)oxy]phenyl}-3-(5-methylisoxazol-3-yl)urea hydrochloride hydrate. The molecular formula is $C_{22}H_{19}ClN_4O_5 \bullet HCl \bullet H_2O$ and the molecular weight is 509.34 Daltons. The chemical structure is:



- Tivozanib hydrochloride, the active ingredient, is a white to light brown powder that is practically insoluble in water (0.09 mg/mL).
- FOTIVDA 1.34 mg capsule contains 1.5 mg of tivozanib hydrochloride (equivalent to 1.34 mg tivozanib) with inactive ingredients: mannitol and magnesium stearate. Capsule composition: gelatin, titanium dioxide, FDA yellow iron oxide, and Blue SB-6018 (ink).
- FOTIVDA 0.89 mg capsule contains 1.0 mg of tivozanib hydrochloride (equivalent to 0.89 mg tivozanib) with inactive ingredients: mannitol and magnesium stearate. Capsule composition: gelatin, titanium dioxide, FDA yellow iron oxide, Blue SB-6018 (ink) and Yellow SB-3017 (ink). The Yellow SB-3017 ink contains FD&C Yellow No.5 (tartrazine).

Item	Information Provided in NDA
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(12), 21 CFR 201.100(b)(5)(iii), 21 CFR 314.94(a)(9)(iii), and 21 CFR 314.94(a)(9)(iv))	
Proprietary name and established name	Provided
Dosage form and route of administration	NA
Active moiety expression of strength with equivalence statement (if applicable)	Yes
For parenteral, otic, and ophthalmic dosage forms, include the quantities of all inactive ingredients [see 21 CFR 201.100(b)(5)(iii), 21 CFR 314.94(a)(9)(iii), and 21 CFR 314.94(a)(9)(iv)], listed by USP/NF names (if any) in alphabetical order (USP <1091>)	NA
Statement of being sterile (if applicable)	NA
Pharmacological/ therapeutic class	Provided
Chemical name, structural formula, molecular weight	Provided
If radioactive, statement of important nuclear characteristics.	NA
Other important chemical or physical properties (such as pKa or pH)	Provided

5. ***Section 16 How Supplied/Storage and Handling***

FOTIVDA (tivozanib) capsules, for oral use are supplied as follows:

Capsule Strength	Opaque Capsule Color	Capsule Markings	Pack Size	NDC Code
Tivozanib 1.34mg (equivalent to 1.5 mg tivozanib hydrochloride)	Bright yellow cap and body	"TIVZ" imprinted with dark blue ink on cap; "SD" imprinted with dark blue ink on body "	Bottles of 21	NDC 45629-101-02
Tivozanib 0.89mg (equivalent to 1.0 mg tivozanib hydrochloride	Dark blue cap and bright yellow body	"TIVZ" imprinted with yellow ink on cap; "LD" imprinted with dark blue ink on body	Bottles of 21	NDC 45629-100-02

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

Keep out of reach of children.

Item	Information Provided in NDA
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(17))	
Strength of dosage form	Provided
Available units (e.g., bottles of 100 tablets)	Provided
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	Provided
Special handling (e.g., protect from light)	Yes (Keep out of reach of children)
Storage conditions	Provided
Manufacturer/distributor name (21 CFR 201.1(h)(5))	Provided

Reviewer's Assessment of Package Insert: *Adequate*

II. Labels:

1. ***Container and Carton Labels***

(b) (4)

2. *Carton Label*

Information request: The NDA labeling module 1.14, only has the labels for the 1.34 mg and 0.89 mg strengths bottles. Since the bottles will be packed into a cardboard outer carton, provide the labeling for the cartons of 1.34 mg and 0.89 mg strengths.

Response to information request: There is no secondary outer package container (cartons and carton labels) planned for tivozanib. The package insert and accompanying patient information leaflet will be affixed and secured to the bottle using glue that complies with 21 CFR 175.105. The finished drug product will then be placed into a cardboard outer shipping container (b) (4) A label will be affixed to the shipper. The applicant provided full and partial shipper labels.

Following is the information on shipping label.

(b) (4)

Reviewer's Assessment of Labels: ***Adequate***
The Agency does not review shipping container labels. The proposed container labels are acceptable.

Clinical, DMEPA and the labeling reviewer, William Pierce recommended the applicant to add the following warning on FOTIVDA 0.89 mg drug product bottle label, "**Contains color additives including FD&C Yellow No. 5 (tartrazine)".** The response is expected on December 7th, 2020.

List of Deficiencies:

Overall Assessment and Recommendation:

Primary Labeling Reviewer Name and Date: Rohit V. Tiwari, Ph.D. 12/02/2020

Secondary Reviewer Name and Date: Anamitro Banerjee, Ph.D. 12/02/2020

Rohit Tiwari

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Anamitro Banerjee

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Date: 12/07/2020 08:55:42AM
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/s/

XIAOHONG CHEN
02/17/2021 11:11:50 AM

ONDQA BIOPHARMACEUTICS REVIEW

NDA#:	**204-408/S-000**
Submission Date:	9/27/2012, 4/22/2013
Drug Name:	Tivopath (Tivozanib Hydrochloride Capsules)
Formulation:	Capsules
Strength:	1 and 1.5 mg
Applicant:	AVEO Pharmaceuticals
Reviewer:	John Duan, Ph.D.
Submission Type:	Original NDA 505(b)(1)

SYNOPSIS

Submission: The tivozanib hydrochloride drug product submitted in NDA 204-408 is an oral, immediate release, hard gelatin capsule proposed for the treatment of patients with advanced renal cell carcinoma.

Review: The Biopharmaceutics review is focused on the dissolution method, the acceptance criterion of dissolution, and the similarity between the to-be-marketed and the clinical formulations. The proposed dissolution acceptance criterion of Q= (b)(4)% at (b)(4) minutes is not acceptable. The dissolution data support a dissolution acceptance criterion of Q= (b)(4)% at (b)(4) minutes, which is recommended to be implemented. The dissolution profile comparison data in three media (pH 1.2, 4.5 and 6.8) showed similarity between the to-be-marketed and the clinical formulations.

RECOMMENDATION

At this time of the review process, ONDQA-Biopharmaceutics has not yet discussed with the Applicant their recommendation for the final dissolution acceptance criterion and therefore NDA 204-408 is not recommended for approval at the present time. The following comment should be conveyed as appropriate to the Applicant.

COMMENT

Your proposed dissolution acceptance criterion (Q= (b)(4)% at (b)(4) minutes) is not supported by the provided dissolution data and is not acceptable. The data support a dissolution acceptance criterion of Q = (b)(4)% at (b)(4) minutes for your product. Implement this criterion at release and on stability. When your NDA is resubmitted, please include the revised specifications table for the drug product with the updated dissolution acceptance criterion.

_____ _____

John Duan, Ph.D. Date
Reviewer
ONDQA Biopharmaceutics

_____ _____

Angelica Dorantes, Ph.D. Date
Team Leader
ONDQA Biopharmaceutics

cc: NDA 204-150/*DARRTS*

BIOPHARMACEUTICS EVALUATION

1. Introduction

Tivozanib hydrochloride is an inhibitor of all three Vascular Endothelial Growth Factor (VEGF) receptors (VEGFR-1, 2 and 3). The tivozanib hydrochloride drug product is an oral, immediate release, hard gelatin capsule that is filled with (b) (4) excipients and tivozanib hydrochloride drug substance. The drug product is manufactured in two strengths: 1.0 mg and 1.5 mg (tivozanib hydrochloride). A size "4" hard gelatin capsule is used for both the 1.0 mg and the 1.5 mg strengths. The application seeks approval for tivozanib hydrochloride for the treatment of patients with advanced renal cell carcinoma. The recommended dose of tivozanib hydrochloride is one 1.5 mg oral dose taken once daily, on a schedule of 3 weeks on treatment followed by 1 week off.

2. The Composition of the Drug Product

The compositions of the 1 and 1.5 mg strengths are shown in the following table.

Component	Quality Standard[1]	Function	Amount per Capsule			
			1.0 mg[2]		1.5 mg[3]	
			mg	%	mg	%
Tivozanib hydrochloride[4]	In-house	Active Pharmaceutical Ingredient	1.0	1.250	1.5	1.875
Mannitol[4]	USP	(b) (4)				
Magnesium stearate	NF					
		Total weight	80.0	100.0	80.0	100.0
Capsule, hard gelatin, Size 4	In-house	Capsule Shell	1		1	
Capsule Imprint Ink(s)	N/A	N/A	trace amount		trace amount	

1 USP-NF: USP = United States Pharmacopeia; NF = National Formulary
2 Each capsule contains 1.0 mg tivozanib hydrochloride equivalent to 0.89 mg tivozanib (free base).
3 Each capsule contains 1.5 mg tivozanib hydrochloride equivalent to 1.34 mg tivozanib (free base).
4 (b) (4)

The Reviewer's Comments: *The two strengths are proportionally similar.*

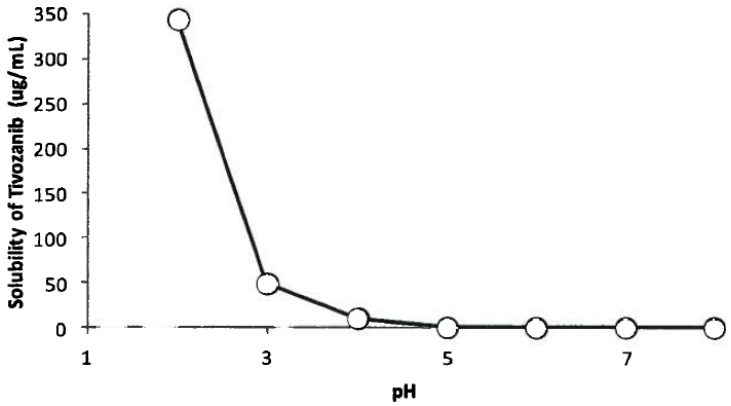
3. General properties of the drug substance

Property	Summary Data
Description	White to light brown powder
Solubility[1,2]	dimethyl sulfoxide: > 100 mg/mL (freely soluble) methanol: 4.32 mg/mL (slightly soluble) ethanol: 8.70 mg/mL (very slightly soluble) water: 0.09 mg/mL (practically insoluble) 0.1 N HCl: < 0.1 mg/mL (practically insoluble) Phosphate Buffer pH 7: < 0.1 mg/mL (practically insoluble) 0.1 N NaOH: < 0.1 mg/mL (practically insoluble) octanol: < 0.2 mg/mL (practically insoluble)

Melting range[3]	181 – 193 °C (followed by decomposition)
pKa	5.9
Hygroscopicity	The drug substance is not hygroscopic.
Polymorphism	(b) (4)
Chirality	There are no chiral centers in the molecule.
Crystallinity	Photomicroscopy indicates that drug substance (b) (4)
Thermal Properties	Differential scanning calorimetry (DSC) analysis shows a broad endothermic peak at approximately 130 °C that correlates with loss of water or solvent, an endothermic onset at approximately 181 °C that indicates the start of melting and an endothermic peak at approximately 190 °C indicative of melting. Thermogravimetric analysis (TGA) showed a 3.6% decrease in weight up to 150 °C which is consistent with the theoretical value for water for the monohydrate form of the drug substance.
Partition coefficient (Log P) (octanol:water)[4]	4.09 (at 40 °C)

1 Solubility values were determined at 25 C.
2 USP solubility definitions (USP General Notices 5.30):
< 0 1 mg/mL: practically insoluble, 0.1 – 1 mg/mL: very slightly soluble, 1 – 10 mg/mL: slightly soluble,
10 - 33 mg/mL: sparingly soluble, 33 – 100 mg/mL: soluble, 100 - 1000 mg/mL: freely soluble
3 The melting range was determined by differential scanning calorimetry and hot stage microscopy.
4 Log P was determined using HPLC in accordance with OECD Guideline 1171.

The pH-solubility profile is shown in the following figure. When 900 mL of dissolution medium is used for 1.5 mg capsules, at least 5 ug/mL of solubility of Tivozanib is required for sink condition. Therefore, lower pH should be selected to achieve sink condition. However, in the acidic media, the solution became viscous and it was difficult to filter the solution.



The Reviewer's Comments: *Although the aqueous solubility of the drug substance is low, the drug loading is low. Therefore, the sink condition can be met in 900 mL dissolution medium and the usage of surfactant in dissolution medium needs to be discussed.*

4. Dissolution Method Development

(b) (4)

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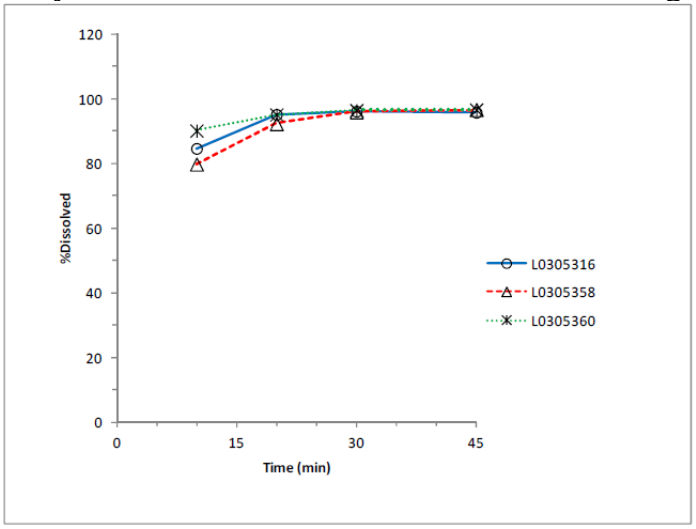
(b) (4)

The following conditions are proposed for the dissolution of the drug product.

Apparatus:	USP. Apparatus 2 (Rotating Paddle)
Paddle Speed:	50 rpm
Medium Temp:	37 °C
Medium:	1 mM HCl with 0.5% w/v Sodium Dodecyl Sulfate (SDS)
Volume:	900 mL
Sample Time:	(b) (4)
Sample Volume:	
Sample Filters:	
Sinkers:	

The dissolution profile data and plots for the registration stability batches of 1.0 mg and 1.5 mg strengths at time zero are shown in the following figure and tables.

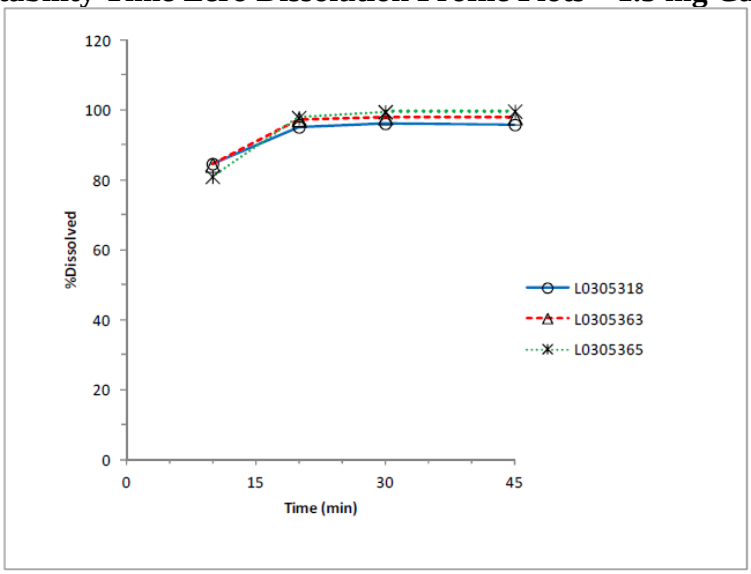
Registration Stability Time Zero Dissolution Profile Plots – 1.0 mg Capsules



Registration Stability Time Zero Dissolution Profile Plots – 1.0 mg Capsules

Vessel Number	Percent Dissolved Results (%)													
	Lot L0305316					Lot L0305358					Lot L0305360			
	Timepoints (min)													
	10	20	30	45		10	20	30	45		10	20	30	45
1	(b) (4)													
2														
3														
4														
5														
6														
Mean (%)	85	94	97	97		80	92	96	97		90	95	97	97
RSD (%)	26	8	3	2		26	6	3	4		3	1	1	1

Registration Stability Time Zero Dissolution Profile Plots – 1.5 mg Capsules



Registration Stability Time Zero Dissolution Profile Data – 1.5 mg Capsules

Vessel Number	Percent Dissolved Results (%)													
	Lot L0305318					Lot L0305363					Lot L0305365			
	Timepoints (min)													
	10	20	30	45		10	20	30	45		10	20	30	45
1	(b) (4)													
2														
3														
4														
5														
6														
Mean (%)	85	95	96	96		84	97	98	98		81	98	100	100
RSD (%)	15	2	1	2		21	2	1	1		22	2	2	1

The proposed acceptance criterion is Q = (b) (4)% in (b) (4) minutes.

The Reviewer's Comments: *The registration batches showed rapid dissolution with more than 92% dissolved at 20 minutes. However, the proposed dissolution acceptance criterion is Q=* (b) (4)*% at* (b) (4) *minutes, which is not supported by the data and is not acceptable.*

An information request was issued on 14 February 2013 and on February 22, 2013, a teleconference was held with the Applicant to provide further clarification on the Agency's questions relating to the proposed dissolution method. The following agreement was reached for the dissolution method and acceptance criterion.

> *To support the approval of the dissolution method and acceptance criterion for their product, the Applicant agreed to do either of the following:*
>
> *a. Modify the surfactant concentration and develop a new dissolution method more discriminating.*
>
> *Or,*
>
> *b. Using the currently proposed dissolution method, provide data for the 15 minute time point in addition to 10, 20, and 30 minutes.*

In the response dated 4/22/2013, the Applicant provided data for the 15 minute time point in addition to 10, 20, and 30 minutes. Data at 45 minutes was also generated for additional information. Dissolution profile analysis was performed for three batches each of the 1.0 mg and 1.5 mg strengths for both clinical and registration batches of tivozanib hydrochloride capsules. The proposed dissolution method was used for this analysis, i.e., USP Apparatus 2 (Paddles) with a rotation speed of 50 rpm and 900 mL of 1 mM HCl, 0.5% sodium dodecyl sulfate (SDS) as the dissolution medium. The following table shows the batches used in the study.

Lot Number[1]	Manufacturer	Date of Manufacture	Theoretical Batch Size (capsules)	Label Claim[2]	Batch Use
1.0 mg Clinical Capsule Batches			(b) (4)		
L0309011 (334493)	Aptuit, Livingston, Scotland, UK	14-Jan-2010		1.0 mg	Clinical
L0306838 (362053)	Aptuit, Livingston, Scotland, UK	21-Apr-2011		1.0 mg	Clinical
L0400830	Catalent (formerly Aptuit), Kansas City, Missouri, USA	04-Dec-2012		1.0 mg	Clinical
1.5 mg Clinical Capsule Batches					
L0306757 (362055)	Aptuit, Livingston, Scotland, UK	22-Apr-2011		1.5 mg	Clinical
L0306758 (362056)	Aptuit, Livingston, Scotland, UK	25-Apr-2011		1.5 mg	Clinical
L0400831	Catalent (formerly Aptuit), Kansas City, Missouri, USA	05-Dec-2012		1.5 mg	Clinical
1.0 mg Registration Capsule Batches					
L0305316	Catalent (formerly Aptuit), Kansas City, Missouri, USA	21-Apr-2011		1.0 mg	Registration
L0305358	Catalent (formerly Aptuit), Kansas City, Missouri, USA	20-Apr-2011		1.0 mg	Registration
L0305360	Catalent (formerly Aptuit), Kansas City, Missouri, USA	26-Apr-2011		1.0 mg	Registration
1.5 mg Registration Capsule Batches					
L0305318	Catalent (formerly Aptuit), Kansas City, Missouri, USA	02-May-2011		1.5 mg	Registration
L0305363	Catalent (formerly Aptuit), Kansas City, Missouri, USA	04-May-2011		1.5 mg	Registration
L0305365	Catalent (formerly Aptuit), Kansas City, Missouri, USA	04-May-2011		1.5 mg	Registration

[1] The clinical capsules manufactured at Aptuit, Livingston, UK have two associated batch numbers: the original number, in parenthesis, that was assigned by the manufacturing site and a second number that was assigned by Catalent, Kansas City, USA where the product is currently being stored.

[2] Each capsule contains either 1.0 mg tivozanib hydrochloride equivalent to 0.89 mg tivozanib (free base) or 1.5 mg tivozanib hydrochloride equivalent to 1.34 mg tivozanib (free base).

The results for 1.5 mg strength registration batches are shown in the following table.

Timepoint (min)	Lot Number		
	L0305318 Registration	L0305363 Registration	L0305365 Registration
	%Dissolved		
10	(b) (4)		
Mean (%)	86	85	88
Standard Deviation	6.3	26.8	22.6
RSD (%)[1]	7.3	31.4	25.8
15	(b) (4)		
Mean (%)	96	95	95
Standard Deviation	2.0	14.3	15.3
RSD (%)	2.1	15.0	16.1
20	(b) (4)		
Mean (%)	99	99	99
Standard Deviation	2.5	5.5	7.8
RSD (%)	2.5	5.6	7.8
30	(b) (4)		
Mean (%)	99	103	103
Standard Deviation	1.6	1.2	1.0
RSD (%)	1.6	1.2	1.0
45	(b) (4)		
Mean (%)	100	103	103
Standard Deviation	2.1	1.5	1.1
RSD (%)	2.1	1.4	1.1

[1] RSD = relative standard deviation

Timepoint (min)	1.5 mg Registration Capsule Lot Number					
	L0305318		L0305363		L0305365	
	Mean %Dissolved	RSD (%)	Mean %Dissolved	RSD (%)	Mean %Dissolved	RSD (%)
10	86	7.3	85	31.4	88	25.8
15	96	2.1	95	15.0	95	16.1
20	99	2.5	99	5.6	99	7.8
30	99	1.6	103	1.2	103	1.0
45	100	2.1	103	1.4	103	1.1

The results for 1.5 mg strength clinical batches are shown in the following table.

Timepoint (min)	Lot Number		
	L0306757 Clinical	L0306758 Clinical	L0400831 Clinical
	%Dissolved		
10	(b) (4)		
Mean (%)	77	83	79
Standard Deviation	15.0	4.9	15.5
RSD (%)[1]	19.5	5.9	19.6
15	(b) (4)		
Mean (%)	91	92	95
Standard Deviation	2.8	1.4	3.5
RSD (%)	3.1	1.5	3.7
20	(b) (4)		
Mean (%)	94	94	98
Standard Deviation	2.1	0.9	1.5
RSD (%)	2.3	1.0	1.5
30	(b) (4)		
Mean (%)	95	96	99
Standard Deviation	2.1	1.1	1.4
RSD (%)	2.3	1.2	1.4
45	(b) (4)		
Mean (%)	95	96	99
Standard Deviation	2.2	1.3	1.3
RSD (%)	2.3	1.3	1.3

[1] RSD = relative standard deviation

Timepoint (min)	1.5 mg Clinical Capsule Lot Number					
	L0306757		L03056758		L0400831	
	Mean %Dissolved	RSD (%)	Mean %Dissolved	RSD (%)	Mean %Dissolved	RSD (%)
10	77	19.5	83	5.9	79	19.6
15	91	3.1	92	1.5	95	3.7
20	94	2.3	94	1.0	98	1.5
30	95	2.3	96	1.2	99	1.4
45	95	2.3	96	1.3	99	1.3

The results for 1.0 mg strength registration batches are shown in the following table.

Timepoint (min)	Lot Number		
	L0305316 Registration	L0305358 Registration	L0305360 Registration
	%Dissolved		
10	(b) (4)		
Mean (%)	98	97	96
Standard Deviation	3.9	1.9	3.4
RSD (%)[1]	4.0	2.0	3.5
15	(b) (4)		
Mean (%)	101	100	100
Standard Deviation	3.8	1.5	1.7
RSD (%)	3.8	1.5	1.7
20	(b) (4)		
Mean (%)	101	100	101
Standard Deviation	3.7	1.6	1.9
RSD (%)	3.7	1.6	1.9
30	(b) (4)		
Mean (%)	103	100	101
Standard Deviation	3.6	1.7	1.6
RSD (%)	3.5	1.7	1.6
45	(b) (4)		
Mean (%)	105	101	101
Standard Deviation	2.9	1.6	1.9
RSD (%)	2.8	1.6	1.8

[1] RSD = relative standard deviation

Timepoint (min)	1.0 mg Registration Capsule Lot Number					
	L0305316		L0305358		L0305360	
	Mean %Dissolved	RSD (%)	Mean %Dissolved	RSD (%)	Mean %Dissolved	RSD (%)
10	98	4.0	97	2.0	96	3.5
15	101	3.8	100	1.5	100	1.7
20	101	3.7	100	1.6	101	1.9
30	103	3.5	100	1.7	101	1.6
45	105	2.8	101	1.6	101	1.8

The results for 1.0 mg strength clinical batches are shown in the following table.

Timepoint (min)	Lot Number		
	L0306838 Clinical	L0309011 Clinical	L0400830 Clinical
	%Dissolved		
10	(b) (4)		
Mean (%)	81	82	92
Standard Deviation	13.7	3.4	3.4
RSD (%)[1]	16.8	4.2	3.7
15	(b) (4)		
Mean (%)	93	90	96
Standard Deviation	3.8	2.1	3.6
RSD (%)	4.0	2.3	3.7
20	(b) (4)		
Mean (%)	96	92	98
Standard Deviation	2.2	2.2	3.0
RSD (%)	2.3	2.4	3.1
30	(b) (4)		
Mean (%)	97	94	99
Standard Deviation	1.8	2.7	1.8
RSD (%)	1.8	2.8	1.8
45	(b) (4)		
Mean (%)	97	96	99
Standard Deviation	1.7	2.6	1.7
RSD (%)	1.7	2.7	1.7

[1] RSD = relative standard deviation

Timepoint (min)	1.0 mg Clinical Capsule Lot Number					
	L03056838		L0309011		L0400830	
	Mean %Dissolved	RSD (%)	Mean %Dissolved	RSD (%)	Mean %Dissolved	RSD (%)
10	81	16.8	82	4.2	92	3.7
15	93	4.0	90	2.3	96	3.7
20	96	2.3	92	2.4	98	3.1
30	97	1.8	94	2.8	99	1.8
45	97	1.7	96	2.7	99	1.7

(b) (4)

Consider all these factors, the optimal dissolution conditions seem to be difficult to select. As a compromise, the proposed dissolution conditions are accepted. However, the proposed acceptance criterion of Q= (b) (4) *% at* (b) (4) *minutes is not acceptable. Q=* (b) (4) *minutes is recommended and it should be implemented.*

5. The validation of the analytical method

The validation results of the analytical method are shown in the following table.

Validation Parameter	Acceptance Criteria	Result
Specificity	No interference from the placebo capsules, mobile phase, or dissolution medium greater than 2% of the mean response of the tivozanib working standard	There was no interference (0%) with the tivozanib peak from the placebo capsules, mobile phase, or dissolution medium.
Linearity	The coefficient of correlation (r) is not less than 0.995. The y-intercept is NMT ±3% of the mean peak area response of the working standard concentration. Range: 20% of the 1.0 mg label claim to 120% of the 1.5 mg label claim	Analyst 1: r = 1.000 y-intercept 0.3% of main peak Analyst 2: r = 1.000 y-intercept 0.2% of main peak
Accuracy	The mean percent recovery (n=3) for each spiking level must be between 95% and 105% Spiking levels: 20% of 1.0 mg (0.2 mg) to 120% of 1.5 mg (1.8 mg)	Analyst 1: Range of % recovery$_3$ = 98 - 99% Analyst 2: Range of % recovery$_3$ = 102 - 104%
Precision: Method repeatability	For each analyst, the %RSD of the percent recoveries (n=9) may not exceed 3% for each dosage strength	Analyst 1: 1.0 mg RSD$_9$ = 0.5% 1.5 mg RSD$_9$ = 0.5% Analyst 2: 1.0 mg RSD$_9$ = 0.9% 1.5 mg RSD$_9$ = 0.8%
Precision: Intermediate precision	For each analyst, the % RSD of the mean values at each timepoint must be ≤ 6%. The absolute difference between the mean values at each timepoint of analyst 1 and 2 must be ≤ 10%.	Analyst 1: 1.0 mg 30 min RSD$_6$ = 2.0% 1.0 mg 45 min RSD$_6$ = 2.1% 1.5 mg 30 min RSD$_6$ = 2.9% 1.5 mg 45 min RSD$_6$ = 2.6% Analyst 2: 1.0 mg 30 min RSD$_6$ = 2.3% 1.0 mg 45 min RSD$_6$ = 1.6% 1.5 mg 30 min RSD$_6$ = 1.3% 1.5 mg 45 min RSD$_6$ = 1.6% Analyst Difference: 1.0 mg 30 min = 0.9% 1.0 mg 45 min = 0.8% 1.5 mg 30 min = 1.8% 1.5 mg 45 min = 1.6%
Filter Study	The percent recovery of the filtered aliquots as compared to the unfiltered aliquots must be 97 – 103%	1.0 mg recovery = 100% 1.5 mg recovery = 99%

Solution stability	The mean percent recovery of tivozanib should be 98 – 102% as compared with the initial result for both standard and sample solutions. Storage conditions: ambient, protected from light.	Standard solution: 7 days: 99-100% Sample solutions: 6 days: 99-100%
Dissolution Medium Stability	The pH of the dissolution medium must be within ± 0.05 pH units of the pH at the time of preparation to continue use.	21 days: pH change 0.01
Robustness: Dissolution Parameters	The absolute difference between the mean percent recovery at 45 minutes and the mean value of analyst 1 intermediate sample precision must be within ± 10% when the following method parameters are varied: • Surfactant concentration • Medium HCl concentration • Medium deaeration • Medium temperature • Paddle speed • Paddle height	None of the parameters were determined to be critical to the performance of the method when within the limits of the robustness testing.
Robustness: HPLC Parameters	Each run must meet system suitability requirements. The %RSD of at least 6 injections of the standard and the %RSD of the check standard throughout the run must be NMT 2.0%. The mean percent recovery of the check standard should be 98% - 102% as compared to the mean working standard when the following method parameters are varied: • Flow rate • Detection wavelength • Mobile phase composition	None of the parameters were determined to be critical to the performance of the method when within the limits of the robustness testing.

The Reviewer's Comment: *The analytical method for dissolution testing is adequate.*

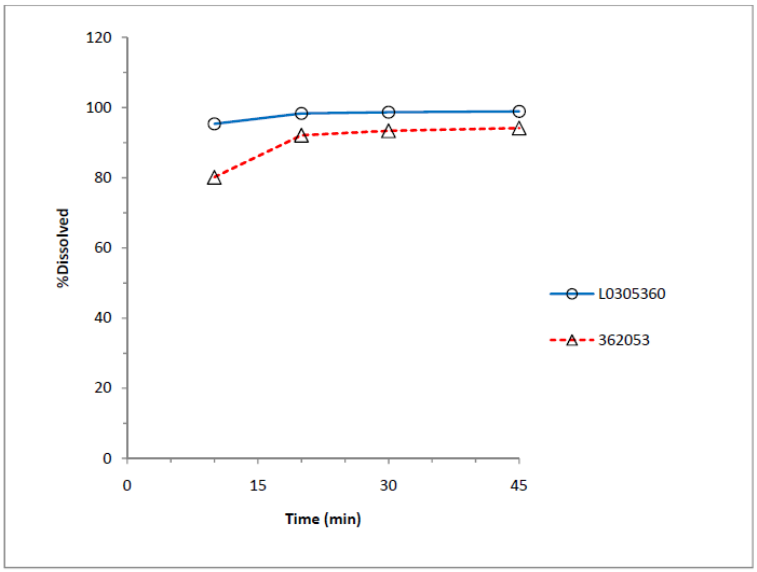
6. The comparison of the clinical formulation and the to-be-marketed formulation

The drug product clinical formulation and manufacturing process were transferred to the proposed commercial site which used the same equipment train and similar process scale. The capsule color was changed from the clinical white capsules to registration capsules colorant of blue/yellow and yellow/yellow for the 1.0 mg and 1.5 mg strengths, respectively. Drug product utilizing the new color capsules were placed on stability. A dissolution profile comparison was performed between the white capsules manufactured at the clinical site and the colored capsules manufactured at the proposed commercial site. The registration dissolution method was used for the analysis. The comparison was conducted using a model independent multivariate confidence region procedure. The dissolution profiles were determined to be similar as shown in the following table and figures.

Dose	Clinical Manufacturing Site Batch Number	Registration Manufacturing Site Batch Number	Upper MSD[1] Confidence Limit	Similarity Limit	Result[2]
1.0 mg	362053	L0305360	4.4349352	4.9033936	Similar
1.5 mg	362055	L0305365	5.7875996	7.848507	Similar

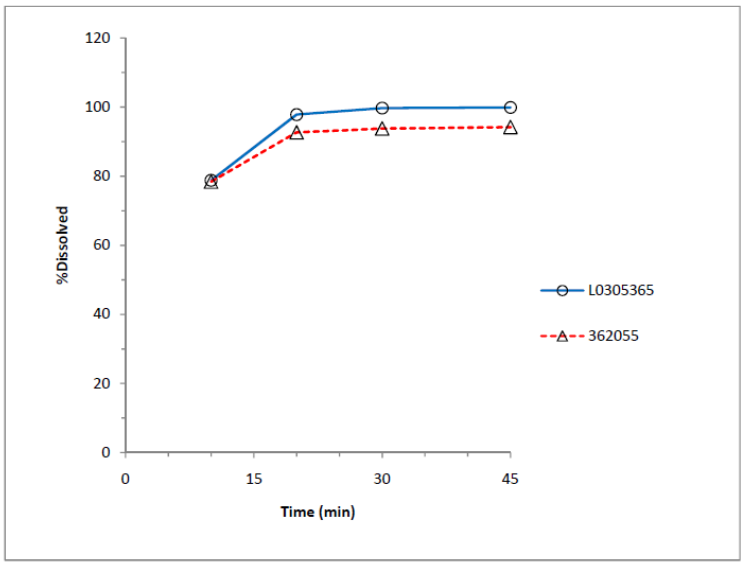
[1] MSD = Multivariate Statistical Distance
[2] Batches are considered similar if the upper limit of the MSD confidence interval is less than the similarity limit.

Figure 1: Comparative Dissolution of Manufacturing Sites – 1.0 mg Capsule



Dissolution Method: 1 mM HCl with 0.5% SDS, 900 mL, 50 rpm paddle speed, n = 12
L0305360: Commercial Manufacturing Site – blue cap/yellow body capsules
362053: Clinical Manufacturing Site – white capsules

Figure 2: Comparative Dissolution of Manufacturing Sites – 1.5 mg Capsule



Dissolution Method: 1 mM HCl with 0.5% SDS, 900 mL, 50 rpm paddle speed, n = 12
L0305365: Commercial Manufacturing Site – yellow/yellow capsules
362055: Clinical Manufacturing Site – white capsules

The Reviewer's Comment: *The method used for dissolution profile comparison is not adequate and therefore the results are not acceptable.*

An information request was issued on 14 February 2013 and on February 22, 2013, a teleconference was held with the Applicant to provide further clarification on the Agency's questions relating to the proposed dissolution method. The following agreement was reached regarding the site change.

> To support the approval of the site change, the Applicant agreed to provide dissolution profile comparison and f2 data (*10, 15, 20, 30, 45,* and 60 minutes, n=12) for the clinical product vs. the to-be-marketed product, using dissolution media without surfactant at pHs 1.2, 4.5, and 6.8 and the same dissolution testing conditions (USP 2 at 50 rpm **or** USP 1 at 100 rpm).
>
> In response to the Applicant's query, FDA responded that a post-marketing commitment is not appropriate, as the link between the clinical and the to-be-marketed formulations must be established before an action can be taken.

The Applicant, in the response dated 4/22/2013, provided dissolution profile analysis for one batch each of 1.0 mg clinical and registration batches and for one batch each of 1.5 mg clinical and registration batches of tivozanib hydrochloride capsules as shown in the following table. The registration batches are representative of the to-be- marketed product. The clinical batches were manufactured at the Aptuit, Livingston United Kingdom site and the registration batches were manufactured at the Catalent facility in Kansas City, Missouri. Each capsule batch was analyzed using Apparatus 2 (Paddles) with a rotation speed of 50 rpm in 900 mL of three different dissolution media: pH 1.2, pH 4.5 and pH 6.8. Capsule sinkers were used and sampling was performed manually. The profile timepoints were: 10, 15, 20, 30, 45 and 60 minutes. Twelve (n = 12) capsules of each capsule batch were analyzed. The dissolution profile data was evaluated for comparability using the f2 similarity factor.

Lot Number[1]	Manufacturer	Date of Manufacture	Theoretical Batch Size (capsules)	Label Claim[2]	Batch Use
362053 (L0306838)	Aptuit, Livingston, Scotland, UK	21-Apr-2011	93,750	1.0 mg	Clinical
362055 (L0306757)	Aptuit, Livingston, Scotland, UK	22-Apr-2011	187,500	1.5 mg	Clinical
L0305360	Catalent (formerly Aptuit), Kansas City, Missouri, USA	26-Apr-2011	187,500	1.0 mg	Registration
L0305365	Catalent (formerly Aptuit), Kansas City, Missouri, USA	04-May-2011	187,500	1.5 mg	Registration

[1] The clinical capsules have two associated batch numbers: the original number that was assigned by the manufacturing site, Aptuit, Livingston, UK, and a second number, in parenthesis, that was assigned by Catalent, Kansas City, USA where the product is currently being stored.

[2] Each capsule contains either 1.0 mg tivozanib hydrochloride equivalent to 0.89 mg tivozanib (free base) or 1.5 mg tivozanib hydrochloride equivalent to 1.34 mg tivozanib (free base).

The results for 1.5 mg and 1.0 mg strengths in pH 1.2 medium are shown in the following tables.

Dissolution Parameters	pH 1.2 USP 2 Paddles, 50 rpm, 900 mL			
Timepoint (min)	1.5 mg Capsule Lot Number			
	362055 (L0306757) Clinical		L0305365 Registration	
	Mean %Dissolved	RSD (%)	Mean %Dissolved	RSD (%)
10	44	12.0	40	56.0
15	52	14.2	48	50.5
20	56	11.0	56	49.9
30	59	10.3	58	47.0
45	66	12.3	64	47.5
60	66	11.8	64	45.7
f_2	78			

Dissolution Parameters	pH 1.2 USP 2 Paddles, 50 rpm, 900 mL			
Timepoint (min)	1.0 mg Capsule Lot Number			
	362053 (L0306838) Clinical		L0305360 Registration	
	Mean %Dissolved	RSD (%)	Mean %Dissolved	RSD (%)
10	43	28.4	53	16.8
15	53	28.7	58	19.6
20	60	28.2	65	18.0
30	63	29.8	69	12.7
45	65	24.9	75	8.3
60	71	26.0	75	10.0
f_2	57			

The results for 1.5 mg and 1.0 mg strengths in pH 4.5 medium are shown in the following tables.

Dissolution Parameters	pH 4.5 USP 2 Paddles, 50 rpm, 900 mL			
Timepoint (min)	1.5 mg Capsule Lot Number			
	362055 (L0306757) Clinical		L0305365 Registration	
	Mean %Dissolved	RSD (%)	Mean %Dissolved	RSD (%)
10	2	23.1	2	81.2
15	2	22.6	3	67.6
20	3	13.4	4	57.6
30	4	14.4	6	50.2
45	6	12.6	7	42.8
60	7	10.5	8	40.4
f_2	91			

Dissolution Parameters	pH 4.5 USP 2 Paddles, 50 rpm, 900 mL			
Timepoint (min)	1.0 mg Capsule Lot Number			
	362053 (L0306838) Clinical		L0305360 Registration	
	Mean %Dissolved	RSD (%)	Mean %Dissolved	RSD (%)
10	2	33.1	4	45.9
15	3	22.2	6	38.4
20	4	21.5	7	39.1
30	6	15.2	10	32.3
45	7	13.0	13	33.7
60	8	14.5	13	35.5
f_2	69			

The results for 1.5 mg and 1.0 mg strengths in pH 6.8 medium are shown in the following tables.

Dissolution Parameters	pH 6.8 USP 2 Paddles, 50 rpm, 900 mL			
Timepoint (min)	1.5 mg Capsule Lot Number			
	362055 (L0306757) Clinical		L0305365 Registration	
	Mean %Dissolved	RSD (%)	Mean %Dissolved	RSD (%)
10	2	183.4	5	116.8
15	1	27.1	4	34.6
20	1	42.5	5	43.3
30	1	35.4	8	109.7
45	1	13.7	6	31.5
60	2	16.2	6	32.5
f_2	67			

Dissolution Parameters	pH 6.8 USP 2 Paddles, 50 rpm, 900 mL			
Timepoint (min)	1.0 mg Capsule Lot Number			
	362053 (L0306838) Clinical		L0305360 Registration	
	Mean %Dissolved	RSD (%)	Mean %Dissolved	RSD (%)
10	1	22.0	5	43.9
15	2	42.9	4	57.0
20	2	25.1	5	52.1
30	2	18.5	8	96.9
45	2	19.7	6	35.5
60	3	22.4	7	33.9
f_2	69			

Reviewer's Comments: *The Reviewer checked the f2 calculations and obtained exactly the same results. It is noted that the data at the 10-minute timepoint had the RSD greater than 20% and the data at all other timepoints had RSD more than 10%. In some comparisons, the clinical lots had higher variability, while in the other comparisons the to-be-marketed formulation had higher variability. This high variability might be due to the low solubility of the drug substance and that there is no any surfactant added. In addition, due to the solubility limitations of the drug substance, the percent dissolved did not reach more than 75% for any of the three dissolution media. Therefore, in spite of the high variability, the results showed the dissolution profile similarity based on the f2 data. The to-be-marketed formulation and the clinical formulation manufactured at the two sites can be considered similar.*

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/s/

JOHN Z DUAN
05/07/2013

ANGELICA DORANTES
05/08/2013