CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

212904Orig1s000

OTHER REVIEW(S)

Clinical Inspection Summary

Date	01/27/2021
From	Michele Fedowitz, MD Karen Bleich, MD Kassa Ayalew, MD, MPH Good Clinical Practice Assessment Branch (GCPAB) Division of Clinical Compliance Evaluation (DCCE) Office of Scientific Investigations (OSI)
To	Elaine Chang, MD Chana Weinstock, MD Jessica Kim, PharmD, Regulatory Project Manager Division of Oncology (DO) Office of Oncologic Diseases (OOD)
BLA #	212904
Applicant	Aveo Pharmaceutical
Drug	Tevozanib
NME (Yes/No)	Yes
Therapeutic Classification	Tyrosine kinase inhibitor
Proposed Indication	Treatment of patients with relapsed or refractory renal cell carcinoma
Consultation Request Date	May 6, 2020
Summary Goal Date	January 31, 2021
Action Goal Date	March 17, 2021
PDUFA Date	March 31, 2021

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Clinical data from Study AV-951-15-303 were submitted to the Agency in support of a New Drug Application (NDA 212904) for tevozanib for the above proposed indication. Four clinical investigators (Drs. Ornstein (Site 101), Pal (Site 118), Hauke (Site 124), and Kollmannsberger (Site 201)) and the study sponsor (Aveo Pharmaceuticals) were selected for clinical inspections. The inspections of Drs. Kollmannsberger and Pal were conducted as remote regulatory assessments due site and/or travel restrictions related to the COVID-19 pandemic. The inspections of Dr. Ornstein, Dr. Hauke, and Aveo Pharmaceuticals were conducted on-site.

Dr. Pal had been suspended from study enrollment by the sponsor for a period of 7 months due to non-compliance with the transcription of source subject data to the eCRF. No regulatory violation could be issued to Dr. Pal due to the remote nature of the assessment. Aveo's oversight of Dr. Pal was adequate, including daily oversight during the period of non-compliance. There was no evidence of harm to subjects or data integrity related to the delay in

data transcription.

The onsite inspections of Drs. Ornstein and Hauke and remote investigation of Dr. Kollmannsberger revealed no significant findings. There was no evidence of underreporting of serious adverse events or significant protocol deviations. Based on the results of these inspections, the study appears to have been conducted adequately and the data generated by the inspected clinical investigators and the sponsor appear to be acceptable in support of the NDA.

II. BACKGROUND

AVEO Pharmaceuticals Inc. seeks approval of tivozanib for the treatment of patients with relapsed or refractory renal cell carcinoma (RCC). In support of the NDA, the Applicant submitted clinical data from Study **AV-951-15-303** (NCT02627963), titled **"**A Phase 3, Randomized, Controlled, Multi-Center, Open-Label Study to Compare Tivozanib Hydrochloride to Sorafenib in Subjects with Refractory Advanced Renal Cell Carcinoma."

Study Design:
Study AV-951-15-303 is a phase 3, open label, randomized, controlled, parallel arm, multicenter study comparing tivozanib with sorafenib in subjects with refractory, advanced renal cell carcinoma.

Major inclusion criteria include adult subjects with

- histologically or cytologically confirmed renal cell carcinoma (RCC) with a clear cell component,
- measurable disease per RECIST 1.1,
- ECOG performance status of 0 or 1,
- life expectancy ≥3 months,
- failed 2 or 3 prior systemic regimens, including a TKI other than sorafenib or tivozanib

Subjects were consented, then screened. If eligibility criteria were met, subjects were randomized 1:1 to receive tivozanib or sorafenib in 4 week cycles.

Treatment began within 14 days of randomization. Tivozanib 1.5 mg/day was administered orally 3 weeks on, 1 week off; and sorafenib was administered orally 400 mg BID continuously throughout each 4-week cycle.

The primary objective was to compare the progression free survival (PFS) of subjects with refractory advanced RCC randomized to treatment with tivozanib or sorafenib as assessed by blinded independent radiological review (IRR) of computerized tomography (CT) or magnetic resonance imaging (MRI). The secondary objective was to compare the overall survival (OS) of subjects randomized to treatment with tivozanib or sorafenib.

Subjects underwent disease assessment at screening (within 30 days prior to first dose of study drug) and every 8 weeks following Cycle 1, Day 1 until documented radiological disease progression and confirmation by independent radiology review. Response was determined by

RECIST (Version 1.1) criteria.

The first subject was enrolled on May 24, 2016 and the last patient was randomized on October 4, 2018. The primary analysis for this NDA was October 4, 2018 and the overall survival and safety cut-off date was August 15, 2019. A total 343 subjects received a study treatment.

III. RESULTS

1. **Dr. Moshe Ornstein (CI Site 101)**
   Cleveland Clinic Foundation
   Taussig Cancer 9500 Euclid Avenue
   Cleveland, OH 44195
   Inspection dates: August 31 – September 4, 2020

   This investigator was inspected as a surveillance inspection for Study AV-951-15-303. This was the first FDA inspection for this investigator.

   The enrollment logs inspected at the site were consistent with the data listings. At the time of the data cutoff, the investigator site had screened 7 subjects and enrolled 6 (Subject (b) (6) was a screen failure due to brain metastases being present). Four subjects were randomized to the study drug (Subjects (b) (6)) and two were randomized to placebo (Subjects (b) (6)). Subjects (b) (6) had discontinued study treatment due to disease progression and Subject (b) (6) discontinued due to disease progression after data cutoff. At the time of the inspection only subject (b) (6) is alive; all other subjects have died due to disease progression.

   The inspection reviewed the subject source data for all 6 enrolled subjects and compared them to the data listings. The reviewed subject records included informed consent, eligibility criteria, concomitant medications, adverse events and SAEs, laboratory results, and imaging scans. The inspection also reviewed study records including Form FDA 1572s, financial disclosures, task delegation logs, monitoring logs, IRB communications, investigational product shipping, storage and accountability records, and EDC functionality and audit records.

   The primary endpoint was based on independent review of imaging. The inspection verified that the site correctly sent imaging studies to the IRR according to the protocol. The inspection also reviewed source records, clinical notes and CT scans to confirm clinical disease progression.

   The following adverse events and/or concomitant medications were found in the source documents, but not found in the data listings or EDC, due to transcription errors by site staff:

Table 1: Source data missing from submitted data listings

Subject	Visit	Date	Not reported	
			Adverse Events	Concomitant Medications
(b) (6)	C16D1	11/22/2017	Nasal congestion	Azithromycin
	C26, unscheduled	2/12/2019	Lower extremity edema	Lasix
	C2D1	12/1/2016	Decreased appetite, anorexia	
	C3D1	12/29/2016		
	C2D1	12/28/2016	Decreased appetite	Megace

Reviewer's Comments: There is no evidence of harm to subjects from the failure to transcribe the data in Table 1. The missing data is unlikely to affect the quality of the study data because decreased appetite is a known common (>20%) adverse reaction for tivozanib and the occurrence of lower extremity edema had been previously reported for Subject (b) (6)*. Dr. Ornstein did not receive a regulatory violation because he became the clinical investigator on 9/17/2019, after the occurrence of the transcription errors.*

No additional data discrepancies were identified. There was no observation of underreporting of protocol deviations. No Form FDA 483 was issued to Dr. Ornstein at the conclusion of the inspection.

2. Dr. Christian Kollmannsberger (CI Site 201)
600 West 10th Avenue
Vancouver, British Columbia
Canada
Remote Regulatory Assessment Dates: October 13-26, 2020

A remote regulatory assessment was conducted due to travel restrictions during the Covid-19 pandemic. Video conferencing via WebEx and document sharing via an online platform (Box.com) were utilized for the assessment of Study AV-951-15-303.

All subjects met eligibility criteria and the enrollment logs were consistent with the data listings. There were a total of ten (10) randomized subjects at the site. Four subjects were randomized to the tivozanib arm ((b) (6)) and six subjects to the sorafenib arm ((b) (6) Three subjects are currently on study at the site: Subject (b) (6) is currently on treatment and Subjects (b) (6) are on follow-up for overall survival. Subjects (b) (6) withdrew and Subjects (b) (6) are deceased.

The remote regulatory assessment reviewed redacted source data for all ten randomized subjects with a focus on the 3 subjects randomized to the tivozanib

arm and treated at the site including their treatment notes. (Subject (b) (6) was in the tivozanib arm and transferred to another location and their data not reviewed.) Subject records reviewed included screening and enrollment logs, eligibility documentation, informed consent, CT scan reports, clinic visits notes, adverse events and concomitant medications records. Study records including Form FDA 1572s, signature and delegation log, monitoring logs and records, and Research Ethics Board (REB) approvals were also reviewed.

Documentation of overall survival in the source records was consistent with the data listings. The CT scans for the primary endpoint were submitted in a timely manner to the central reader and the timing of progressive disease was verified with the records provided. The review team could not confirm that all adverse events and protocol deviations were reported due to the limitations of remote assessments and required subject identity redactions, however, no evidence of under-reporting of adverse events or protocol deviations was identified.

The site did not have original copies of initial signed ICFs for Subjects (b) (6) . There were notes indicating the subjects had signed the document at home and failed to fax or email it back. Subject (b) (6) was screened on 2/8/2017; Subject (b) (6) was screened on 8/14/2017. The SOP regarding consent procedures at the site allows for signed ICF collection by fax or email in extenuating circumstances.

Reviewer's comments: The site did not appropriately document informed consent for two subjects. It is not clear why the site did not have the subjects re-sign the consent form at the first study visit after screening when they had failed to email or bring the copy that had been signed at home. A regulatory violation was not issued because of the remote nature of the investigation.

3. Dr. Ralph Hauke (CI Site 124)
8303 Dodge Street
Omaha, NE 68114
United States
Inspection dates: September 14-17, 2020

This investigator was inspected as a surveillance inspection for Study AV-951-15-303. This was the first FDA inspection for this investigator.

The enrollment logs inspected at the site were consistent with the data listings. At the time of data-cutoff, the investigator site had screened 9 subjects and enrolled 2, both to the study drug arm (Subjects (b) (6)). Both subjects were off treatment; Subject (b) (6) died due to disease progression and Subject (b) (6) stopped treatment due to disease progression, is alive, and still being followed.

The inspection reviewed the eligibility criteria for all 9 screened subject and reviewed the source data for both enrolled subjects and compared them to the data listings. The

reviewed subject records included informed consents, progress notes, adverse events, lab results, vital signs, drug return forms and patient pill diaries. The inspection also reviewed study records including Form FDA 1572s, financial disclosures, task delegation logs, monitoring logs, IRB communications, investigational product storage and accountability records and EDC functionality and audit records.

The primary endpoint was based on independent review of imaging. The source data for scans and records was acquired according to the protocol.

No significant data discrepancies were identified between source records at the site and the submitted data listings. Specifically, there was no under-reporting of adverse events or protocol deviations. The inspection found no regulatory violations at the site. No Form FDA 483 was issued to Dr. Hauke at the conclusion of the inspection.

4. Sumanta Pal, M.D (Site 118)
1500 E. Duarte Road
Duarte, CA 91010
USA United States
Remote Regulatory Assessments Date: December 7-15, 2020

A remote regulatory assessment (RRA) was conducted because the medical facility would not allow entry for on-site inspection due to the Covid-19 pandemic. Video conferencing via WebEx and document sharing via an online platform (Box.com) were utilized for the assessment of Study AV-951-15-303.

There were 10 subjects screened and 8 subjects enrolled at the site ((b) (6)). At the time of data cut-off, 5 subjects had died and two subjects died after the cut-off ((b) (6)). At the time of the RRA, one subject was alive but had discontinued treatment due to progressive disease (Subject (b) (6)).

The remote regulatory assessment reviewed data for all 8 subjects. It included a review of screening and enrollment logs, eligibility, informed consent forms, CT scan reports, clinic visits notes, a sampling of adverse events, protocol deviations, and concomitant medications, investigational product administration and accountability; as well as the study records including regulatory binders, financial disclosures and Form FDA 1572s, delegation of authority logs, staff training logs, monitoring visit records, IRB approvals and communications.

The primary endpoint was based on independent review of imaging. The regulatory assessment verified that the site sent all on protocol and unscheduled scans to central imaging. There was no discrepancy between the dates of scans performed at the site and those sent to the IRR to determine the primary endpoint. The regulatory assessment verified the source data for the secondary endpoint of overall survival (date of death) was consistent with the data listings.

A Spanish translator was used to consent Subject (b) (6), however, there was no IRB-approved oral presentation used by the translator to consent the subject as required by the regulations [§ 50.27(b)(2)]. The site used a Spanish language short-form that was not specific to the trial.

Reviewer's Comments: Dr. Pal was informed of the need to obtain an IRB-approved written summary of the oral presentation to be used when a subject is consented with a short form according to the regulations. No regulatory violation could be issued due to remote regulatory assessment procedures.

A lag in eCRF data entry was noted on a monitoring visit by (b) (4) and escalated to the sponsor on August 24, 2016. The delayed data entry included adverse event follow up entry, subject screening entries, and reconciliation of major protocol deviations, specifically, failure to enter 21 outstanding issues in the 5 enrolled subjects. Dr Pal agreed to a voluntary suspension from screening and enrollment of new subjects on August 31, 2016. The clinical site took 7 months to come into compliance with data entry. For example, Subject (b) (6) experienced the AE of abdominal discomfort on 6/16/2016. The AE was not entered in the EDC until 2/6/2017. In terms of protocol deviations, there was a delay in the reporting of a protocol deviation (failure to obtain CT/MRI of the brain at screening as required by protocol) for Subject (b) (6). The deviation occurred June 22, 2016 but was not reported until June 21, 2017.

Dr. Pal offered the explanation that the site was short-staffed and the study coordinator at the time did not enter the data, because he was out on leave. During the voluntary suspension (8/2016 – 4/2017), the enrolled subjects continued with study visits and treatment. There were no serious adverse events during this time.

Reviewer's Comments: The entry of subject data into the eCRF was delayed for a significant period of time, including in some instances for as long as 8 months. Dr. Pal's explanation for the delay (staffing shortage) is not adequate. Dr. Pal is responsible for the conduct of the study at the site. No regulatory violation could be issued due to remote regulatory assessment procedures. There was no evidence of harm to subjects or to data reliability and integrity related to the delays.

There was no underreporting of protocol deviations or adverse events at the site.

5. Aveo Pharmaceuticals (Sponsor)
75 Sidney Street, 4th Floor
Cambridge, MA 02139
Inspection Dates: 9/21/2020 – 9/30/2020

The firm was inspected previously in January 2013 with an inspectional classification of Voluntary Action Indicated (VAI) for failure, despite repeated efforts, to bring a clinical investigator into compliance.

Records reviewed included organizational charts, standard operating procedures, investigator selection, monitoring plans, monitoring reports, transfer of responsibilities, correspondence, training records, FDA 1572's, financial disclosure forms, electronic case report forms (eCRFs), protocol deviations, protocol adherence, subject protection and ethical oversite, safety plans, adverse events, data management, primary efficacy endpoint and investigational product accountability records.

Review of monitoring records and correspondences between Aveo and (b) (4) (the CRO responsible for monitoring) demonstrated that it took 7 months to bring Site 118 (CI Dr. Pal) into compliance with the prescribed timelines for the entry of source subject data into the eCRF. Specifically, per the monitoring plan, the data from screening visits should be entered into the eCRF within 3 working days after enrollment; and the data entry for study visits was to be completed within 5 working days. The (b) (4) study monitor notified Aveo in August of 2016 that there was a lag in eCRF completion at Site 118 consisting of 21 outstanding issues for 5 subjects including: adverse event follow up, subject screening, and reconciliation of major protocol deviations. On August 31, 2016, the sponsor suspected enrollment at the site until the data had been entered. Aveo and (b) (4) communicated with the PI at least daily until the site was caught up, which occurred in April 2017. The site did not screen or enroll any new subjects during the suspension time.

Reviewer's Comments: The Sponsor's oversight of Site 118 was adequate. The sponsor ensured temporary suspension of enrollment at the site and the daily communication with the site until the site came into compliance with data entry. Dr. Pal's site had a remote regulatory inspection, please see discussion under Site 118.

The inspection found no regulatory violations. No Form FDA 483 was issued.

{See appended electronic signature page}

Michele Fedowitz, M.D.
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

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cc:

Review Division /Division Director/ Harpreet Singh, M.D.
Review Division /Project Manager/ Jessica Kim, PharmD
Review Division/Cross Discipline Team Lead/ Chana Weinstock, MD
Review Division/Clinical Reviewer/ Elaine Chang, MD

OSI/Office Director/Dave Burrow
OSI/DCCE/ Division Director/Ni Khin, M.D.
OSI/DCCE/Branch Chief/Kassa Ayalew, M.D., M.P.H.
OSI/DCCE/Acting Team Leader/Karen Bleich, M.D.
OSI/DCCE/GCP Reviewer/Michele Fedowitz, M.D.
OSI/ GCP Program Analysts/ Joseph Peacock/Yolanda Patague
OSI/Database PM/Dana Walters

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/s/

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MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	December 8, 2020
Requesting Office or Division:	Division of Oncology 1 (DO1)
Application Type and Number:	NDA 212904
Product Name and Strength:	Fotivda (tivozanib) capsules, 0.89 mg and 1.34 mg
Applicant/Sponsor Name:	Aveo Pharmaceuticals, Inc.
OSE RCM #:	2020-662-1
DMEPA Safety Evaluator:	Tingting Gao, PharmD
DMEPA Team Leader (Acting):	Ashleigh Lowery, PharmD, BCCCP

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container labels received on December 7, 2020 for Fotivda. Division of Oncology 1 (DO1) requested that we review the revised container labels for Fotivda (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

2 CONCLUSION

The Applicant implemented all of our recommendations and we have no additional recommendations at this time.

[a] Gao, T. Label and Labeling Review for Fotivda (NDA 212904). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 Aug 3. RCM No.: 2020-662.

Reference ID: 4712952

APPENDIX A. IMAGES OF LABEL AND LABELING RECEIVED ON DECEMBER 7, 2020

Container labels

(b) (4)



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

PATIENT LABELING REVIEW

Date:	November 9, 2020
To:	Jessica Kim, PharmD Regulatory Health Project Manager **Division of Oncology 1 (DO1)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Barbara Fuller, RN, MSN, CWOCN Team Leader, Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Jessica Chung, PharmD, MS Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Emily Dvorsky, PharmD Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Patient Package Insert (PPI)
Drug Name (established name):	FOTIVDA (tivozanib)
Dosage Form and Route:	capsules, for oral use
Application Type/Number:	NDA 212904
Applicant:	Aveo Pharmaceuticals, Inc.

1 INTRODUCTION

On March 31, 2020, Aveo Pharmaceuticals, Inc. submitted for the Agency's review an original New Drug Application (NDA) 212904 for FOTIVDA (tivozanib) capsules. The proposed indication for FOTIVDA (tivozanib) capsules is for the treatment of patients with relapsed or refractory renal cell carcinoma (RCC).

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Oncology 1 (DO1) on April 15, 2020, for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) for FOTIVDA (tivozanib) capsules.

2 MATERIAL REVIEWED

- Draft FOTIVDA (tivozanib) PPI received on March 31, 2020, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on October 29, 2020.
- Draft FOTIVDA (tivozanib) Prescribing Information (PI) received on March 31, 2020, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on October 29, 2020.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level.

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

In our collaborative review of the PPI we:

- simplified wording and clarified concepts where possible
- ensured that the PPI is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the PPI is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The PPI is acceptable with our recommended changes.

5 RECOMMENDATIONS

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

Please let us know if you have any questions.

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BARBARA A FULLER
11/09/2020 02:23:47 PM

LASHAWN M GRIFFITHS
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FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

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

Memorandum

Date: November 9, 2020

To: Elaine Chang, M.D., Medical Officer
Division of Oncology 1 (DO1)

Jessica Kim, Regulatory Project Manager, (DO1)

William Pierce, PharmD, Associate Director for Labeling, (DO1)

From: Emily Dvorsky, PharmD, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Susannah O'Donnell, MPH, RAC, Team Leader, OPDP

Subject: OPDP Labeling Comments for FOTIVDA® (tivozanib) capsules, for oral use

NDA: 212904

In response to DO1 consult request dated April 15, 2020, OPDP has reviewed the proposed product labeling (PI), patient package insert (PPI), and carton and container labeling for the original NDA submission for FOTIVDA® (tivozanib) capsules, for oral use.

Labeling: OPDP's comments on the proposed labeling are based on the draft labeling downloaded from DO1's Sharepoint on November 2, 2020, and are provided below.

A combined OPDP and Division of Medical Policy Programs (DMPP) review will be completed, and comments on the proposed PPI will be sent under separate cover separate cover.

Carton and Container Labeling: OPDP has reviewed the attached proposed carton and container labeling downloaded from DO1's Sharepoint on November 2, 2020, and we do not have any comments.

Thank you for your consult. If you have any questions, please contact Emily Dvorsky at (240)402-4256 or Emily.Dvorsky@fda.hhs.gov.

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/s/

EMILY M DVORSKY
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Interdisciplinary Review Team for Cardiac Safety Studies

QT Study Review

Submission	NDA-212904
Submission Number	001
Submission Date	3/31/2020
Date Consult Received	4/15/2020
Drug Name	Tivozanib hydrochloride (Fotivda)
Indication	Relapsed or refractory renal cell carcinoma
Therapeutic dose	1.5 mg once daily for 21 days with 7 days off treatment (28 days cycle)
Clinical Division	DO1

Note: Any text in the review with a light background should be inferred as copied from the Sponsor's document.

This review responds to your consult dated 4/15/2020 regarding the Sponsor's QT evaluation. We reviewed the following materials:

- Previous IRT review under IND-075547 dated 07/14/2010 in DARRTS (link);
- Previous IRT review under IND-075547 dated 09/13/2010 in DARRTS (link);
- Previous IRT review under IND-075547 dated 04/03/2012 in DARRTS (link);
- Sponsor's clinical study report # AV-951-10-112 (SN0001; link);
- Sponsor's analysis plan # AV-951-10-112 (SN0001; link);
- Sponsor's proposed product label (SN0001; link) and
- Highlights of clinical pharmacology and cardiac safety (SN0003; link).

1 SUMMARY

No large (>20 msec) QTc prolongation effect of tivozanib was detected in this QT assessment. We are reluctant to draw conclusions of lack of an effect in an absence of a positive control or large exposure margin, or an integrated nonclinical safety assessment conduct according to best practices (ICH S7b Q&A 1.1 and 1.2).

The effect of tivozanib was evaluated in an open-label, multiple dose, single arm study in patients with advanced solid tumors (Study # AV-951-10-112). The highest dose evaluated was 1.5 mg once daily for 21 days, which covers the therapeutic exposures of tivozanib (Section 3.1). The data were analyzed using the exposure-response analysis as the primary analysis, which did not suggest that tivozanib is associated with large mean increases in the QTc interval (refer to Section 4.5) – see Table 1 for overall results.

Reference ID: 4673429

Table 1: The Point Estimates and the 90% CIs

ECG Parameter	Treatment	Concentration (ng/mL)	ΔQTCF (msec)	90% CI (msec)
QTc	Tivozanib 1.5 mg*	104.1	6.9	(3.1 to 10.8)

**Administered as once daily dose for 21 days; For further details on the FDA analysis please see Section 4.*

The results from this analysis are supported by the available nonclinical data (Section 3.1.2), categorical analysis (Section 4.4), and by-timepoint analysis (Section 4.5).

1.1 RESPONSES TO QUESTIONS POSED BY SPONSOR

Not applicable.

1.2 COMMENTS TO THE REVIEW DIVISION

Not applicable.

2 RECOMMENDATIONS

2.1 ADDITIONAL STUDIES

Not applicable.

2.2 PROPOSED LABEL

Below are proposed edits to the label submitted to SDN001 (link) from the IRT. Our changes are highlighted (addition, ~~deletion~~). Please note, that this is a suggestion only and that we defer final labeling decisions to the Division.

12.2 Pharmacodynamics Cardiac Electrophysiology At the recommended dose of <Tradename>, (b) (4) -no large mean increases (i.e., 20 msec) in QTc interval was observed.
We propose to use labeling language for this product consistent with the "Clinical Pharmacology Section of Labeling for Human Prescription Drug and Biological Products – Content and Format" guidance.

3 SPONSOR'S SUBMISSION

3.1 OVERVIEW

3.1.1 Clinical

Aveo Pharmaceuticals is developing tivozanib for the treatment of renal cell carcinoma and other advanced solid tumor malignancies. Tivozanib (AV-951, KRN951, Kil9294, CDM, ASP4130; MW: 509.34, hydrochloride monohydrate) is a vascular endothelial growth factor receptor tyrosine kinase inhibitor.

Reference ID: 4673429

The product is formulated as immediate-release capsule formulation containing 1.5 mg tivozanib (as hydrochloride hydrate) for oral administration. The maximum proposed therapeutic dose for the present indication is 1.5 mg once daily (for 21 days on treatment followed by 7 days off treatment; 28-day cycle) and it is also maximum tolerated dose (Study # KRN951/03-B01, solid tumor). The peak concentrations of ~95 ng/mL (Tmax: 3 to 24 h; half-life: 103 to 122 h) are expected at steady-state with the anticipated therapeutic dose (Day 21; Study # AV-951-07-201). Significant accumulation is expected following multiped dosing (1.5 mg once daily; Racc: ~6; Study # AV-951-07-201). During the development, the maximum studied dose is 2 mg once daily for 4 weeks (Cmax: 110 ng/mL in patients with solid tumor; Study # KRN951-03-B01).

Tivozanib exhibits dose proportional pharmacokinetics between dosses 0.5 and 1.5 mg. The human mass balance study indicates that ~80% of the drug (~42% as unchanged drug) is excreted in feces, and ~12% in urine with minimal unchanged drug (Study # AV-951-10-1). No major metabolites were detected in the serum and thus, the Sponsor highlights that it has a low drug interaction potential as a victim drug. Further, the Sponsor claims that there is no apparent relationship between tivozanib pharmacokinetics and renal function. However, higher tivozanib exposures were observed in subjects with impaired hepatic function (AUC: moderate: 2.2-fold; and severe: 3.4-fold) with no significant impact on the peak concentrations.

Previously, the IRT reviewed the Sponsor's QT study protocol under IND-075547 (Study # AV-951-10-112) and it was found to be acceptable (Dt: 09/13/2010 and 04/03/2012). This was an open-label, multiple dose, single arm study evaluating the exposure-response relationship (C-QT) of tivozanib in patients with advanced solid tumors (n=40/50/51; completed/treated/enrolled). Subjects received 1.5 mg (one capsule) dose once daily for 21 days. ECG and PK samples were collected on Day 1, 8 and 21 at the following timepoints: Day 1, 0 h (pre-dose), 2.5, 4, 5, 6, 8, 10 h; Day 2, 0 h (pre-dose); Day 8, 0 h (pre-dose), 2.5, 5, 8 h; Day 21, 0 h (pre-dose), 2.5, 4, 5, 6, 8, 10 and 24 h.

3.1.2 Nonclinical Safety Pharmacology Assessments

Refer to the Sponsor's highlights of clinical pharmacology and clinical safety, the non-clinical overview (m2.4) and the previous IRT review under IND-075547 dated 09/13/2010 in DARRTS. The expected peak concentrations of ~95 ng/mL (Free: 0.95 ng/mL; PPB: ~99%) at steady-state with once daily dosing of 1.5 mg offers higher than 850-fold margin (hERG – no significant inhibition at 1.6 μM).

An in vitro study determined that tivozanib hydrochloride at 0.82 μg/mL produced no human ether-à-go-go related gene (hERG)-related channel tail current inhibition (Study DRZZ1019). This concentration is approximately 9-fold higher than the maximal serum concentration observed after repeated dosing in subjects with RCC (maximum concentration at steady state [Cmax,ss] = 0.09 μg/mL [Study AV-951-07-201]).

Compounds that inhibit hERG currents in vitro have been shown to prolong cardiac action potential and QT interval in humans (Ficker et al, 1998; Kiehn et al, 1996; Mohammad et al, 1997). As tivozanib hydrochloride did not inhibit hERG channels, additional in vitro models evaluating potential cardiac effects were not considered necessary.

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3.2 SPONSOR'S RESULTS

3.2.1 By Time Analysis

The primary analysis for tivozanib was based on exposure-response analysis, please see Section 3.2.3 for additional details.

Reviewer's comment: The Sponsor's by-time descriptive summary does not show large QTcF effect and the results are consistent with reviewer's results. Please see Section 4.3 for details.

3.2.1.1 Assay Sensitivity

Not applicable.

3.2.1.1.1 QT Bias Assessment

Not applicable.

3.2.2 Categorical Analysis

There were no significant outliers per the Sponsor's analysis for QTc (i.e., > 500 msec, HR (>100 bpm and 25% over baseline), PR (>220 msec and 25% over baseline) and QRS (>120 msec and 25% over baseline). One subject experiences ΔQTcF > 60 msec at one time point.

Reviewer's comment: The Sponsor's outlier counts are consistent with reviewer's results. One subject with HR > 100 bpm with <25 % change from based line were included in reviewer's outlier table. Please see Section 4.4 for details.

3.2.3 Exposure-Response Analysis

As a primary analysis, the Sponsor explored PK/PD relationship between concentration of tivozanib and ΔQTcF (change from baseline in QTcF) using a linear mixed-effects model. Serum concentration, intercept and subject were included as random effects. The Sponsor analysis indicated concentration depended increase in ΔQTcF with small positive slope of 0.08464 ($p<0.0006$). The model-predicted ΔQTcF was 8.3 msec (95% CI 12.6 msec) at the mean peak concentrations of tivozanib following 1.5 mg once daily dose. The results of the Sponsor's analysis suggest an absence of significant QTc prolongation at the maximum proposed therapeutic dose.

In summary, the Sponsor claims that no large (> 20 msec) QTc prolongation effect of tivozanib were detected in the QT assessment at the therapeutic dose.

Reviewer's comment: The conclusion of the reviewer's analysis agreed with the Sponsor's conclusion. Please see Section 4.5 for additional details.

3.2.4 Safety Analysis

Overall, 224 TEAEs were reported by 47 subjects (94.0%). The TEAE with the highest reported incidence was hypertension (22 subjects with 28 events). Nineteen of these subjects had reported incidences of hypertension. Twelve SAEs (11 treatment-emergent SAEs) were reported by 10 subjects (9 subjects with treatment emergent SAEs).

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Three of these events were considered to be possibly related or related to study drug. Three SAEs with an outcome of death, none of which were considered to be related to study drug, and all of which were related to disease progression or recurrence, were reported.

Following administration of tivozanib, 1 subject displayed a clinically significant increase in AST, ALT, and total bilirubin levels on Day 21. The Investigator considered these incidences as AEs and as possibly related to study drug. Three subjects displayed an increase in TSH levels, considered by the Investigator to be clinically significant, following administration of tivozanib. Two of these incidences were considered by the Investigator to be related to study drug. Thirty subjects displayed proteinuria during the course of the study, with 16 subjects displaying increase from baseline in urinary protein on Day 21.

Reviewer's comment: None of the events identified to be of clinical importance per the ICH E14 guidelines (i.e., significant ventricular arrhythmias or sudden cardiac death) occurred in this study.

4 REVIEWERS' ASSESSMENT

4.1 EVALUATION OF THE QT/RR CORRECTION METHOD

The Sponsor used QTcF for the primary analysis, which is acceptable as no large increases or decreases in heart rate (i.e. |mean| < 10 bpm) were observed (see Section 4.3.2).

4.2 ECG ASSESSMENTS

4.2.1 Overall

Overall ECG acquisition and interpretation in this study appears acceptable.

4.2.2 QT Bias Assessment

Not applicable.

4.3 BY-TIME ANALYSIS

The statistical reviewer evaluated the ΔQTcF effect using parametric descriptive statistics.

4.3.1 QTc

Figure 1 displays the time profile of ΔQTcF for different treatment groups. The maximum ΔQTcF values by treatment are shown in Table 2.

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Figure 1: Mean and 90% CI of ΔQTcF Timecourse (unadjusted CIs).

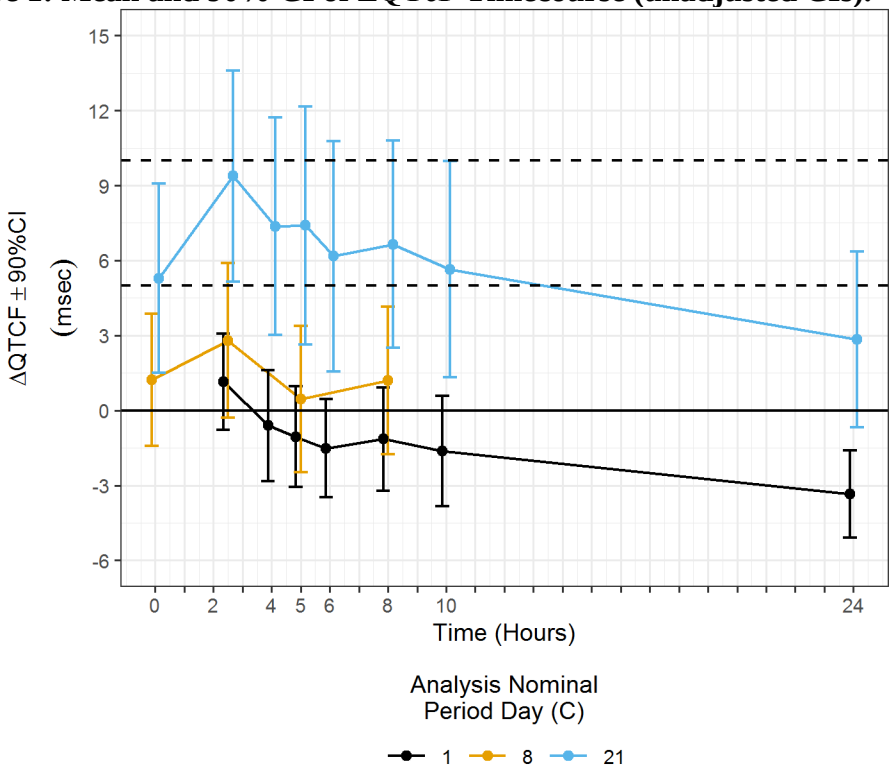


Table 2: The Point Estimates and the 90% CIs Corresponding to the Largest Upper Bounds for ΔQTcF

Analysis Nominal Period Day (C)	N	Time (Hours)	ΔQTCF (msec)	90.0% CI (msec)
21	43	2.500	9.4	(5.2 to 13.6)

4.3.1.1 Assay sensitivity

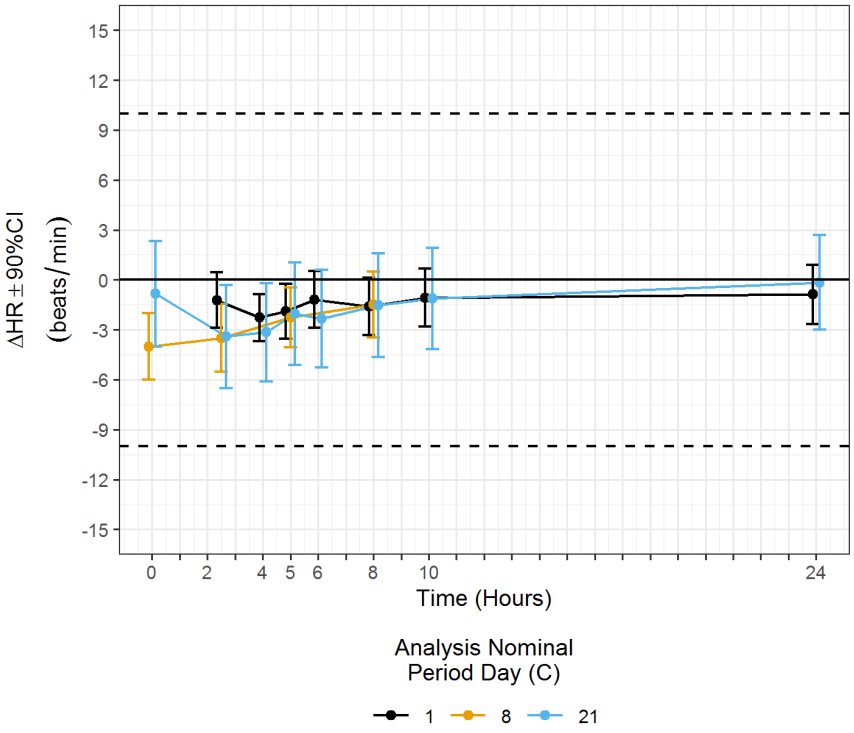
Not applicable.

4.3.2 HR

Figure 2 displays the time profile of ΔHR for different treatment groups.

Reference ID: 4673429

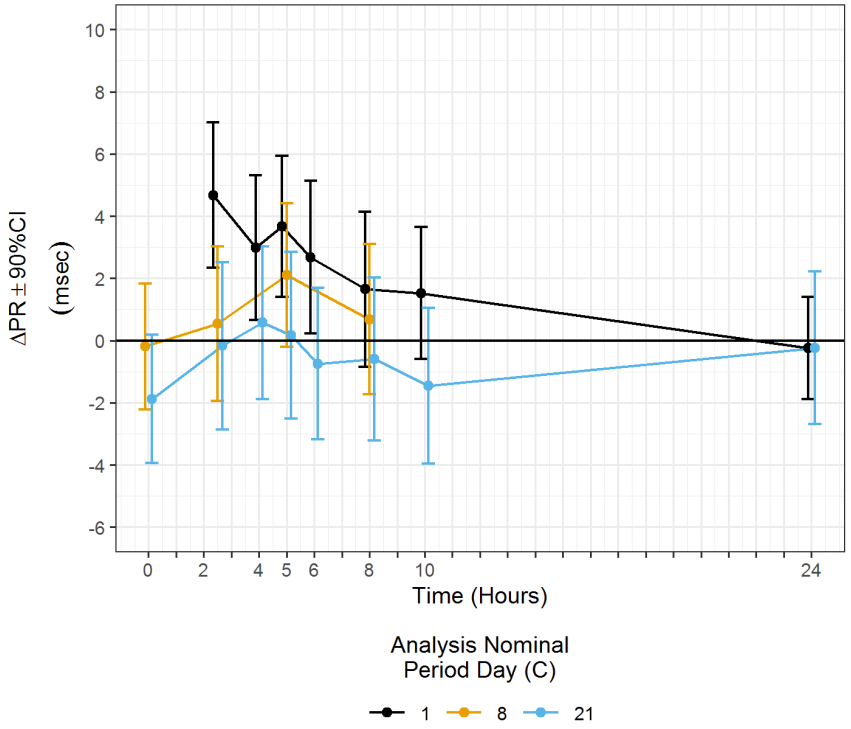
Figure 2: Mean and 90% CI of ΔHR Timecourse



4.3.3 PR

Figure 3 displays the time profile of ΔPR for different treatment groups.

Figure 3: Mean and 90% CI of ΔPR Timecourse

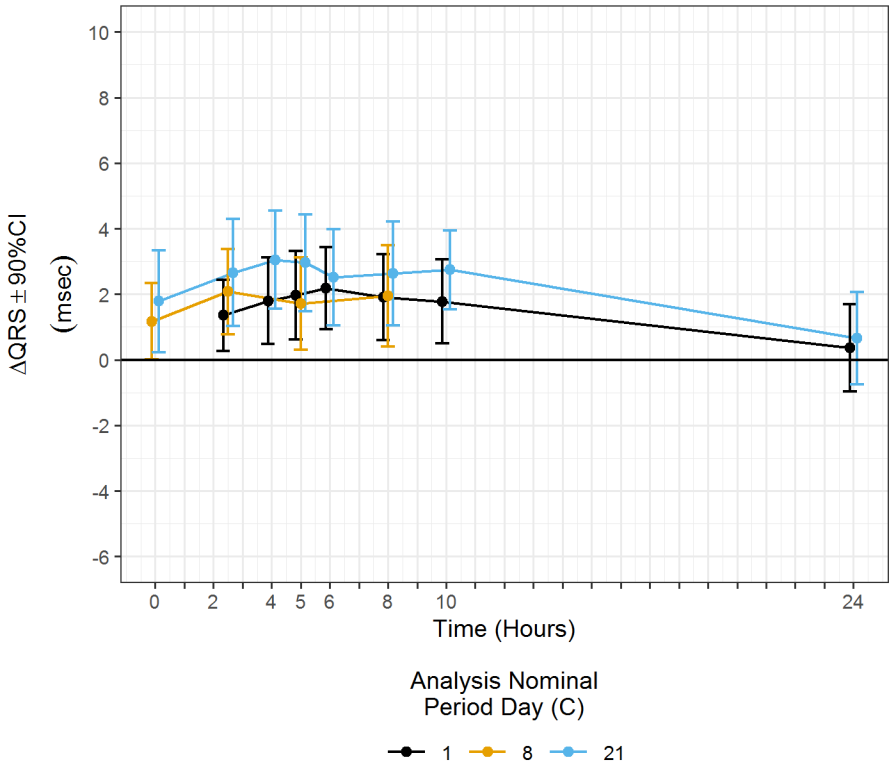


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4.3.4 QRS

Figure 4 displays the time profile of ΔQRS for different treatment groups.

Figure 4: Mean and 90% CI of ΔQRS Timecourse



4.4 CATEGORICAL ANALYSIS

Categorical analysis was performed for different ECG measurements either using absolute values, change from baseline or a combination of both. The analysis was conducted using the safety population and includes both scheduled and unscheduled ECGs.

4.4.1 QTc

No subject had QTcF >500 msec in the study.

Table 3 lists the categorical analysis results for ΔQTcF (less than 30 msec, between 30 and 60 and greater than 60 msec). One subject who received tivozanib 1.5 mg QD experienced ΔQTcF > 60 msec at one time point.

Table 3: Categorical Analysis for ΔQTcF

	Total (N)		Value <= 30 msec		30 msec < Value <= 60 msec		Value > 60 msec	
Actual Treatment	**# Subj.**	**# Obs.**	**# Subj.**	**# Obs.**	**# Subj.**	**# Obs.**	**# Subj.**	**# Obs.**
tivozanib 1.5 mg QD	50	892	43 (86.0%)	861 (96.5%)	6 (12.0%)	30 (3.4%)	1 (2.0%)	1 (0.1%)

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4.4.2 HR

Table 4 lists the categorical analysis results for maximum HR (<100 bpm and >100 bpm). One subject received tivozanib 1.5 mg QD experienced HR > 100 bpm.

Table 4: Categorical Analysis for HR

Actual Treatment	Total (N)		Value <= 100 beats/min		Value > 100 beats/min	
	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
tivozanib 1.5 mg QD	50	892	49 (98.0%)	880 (98.7%)	1 (2.0%)	12 (1.3%)

4.4.3 PR

No subject had PR >120 msec with 25% increase over baseline in the study.

4.4.4 QRS

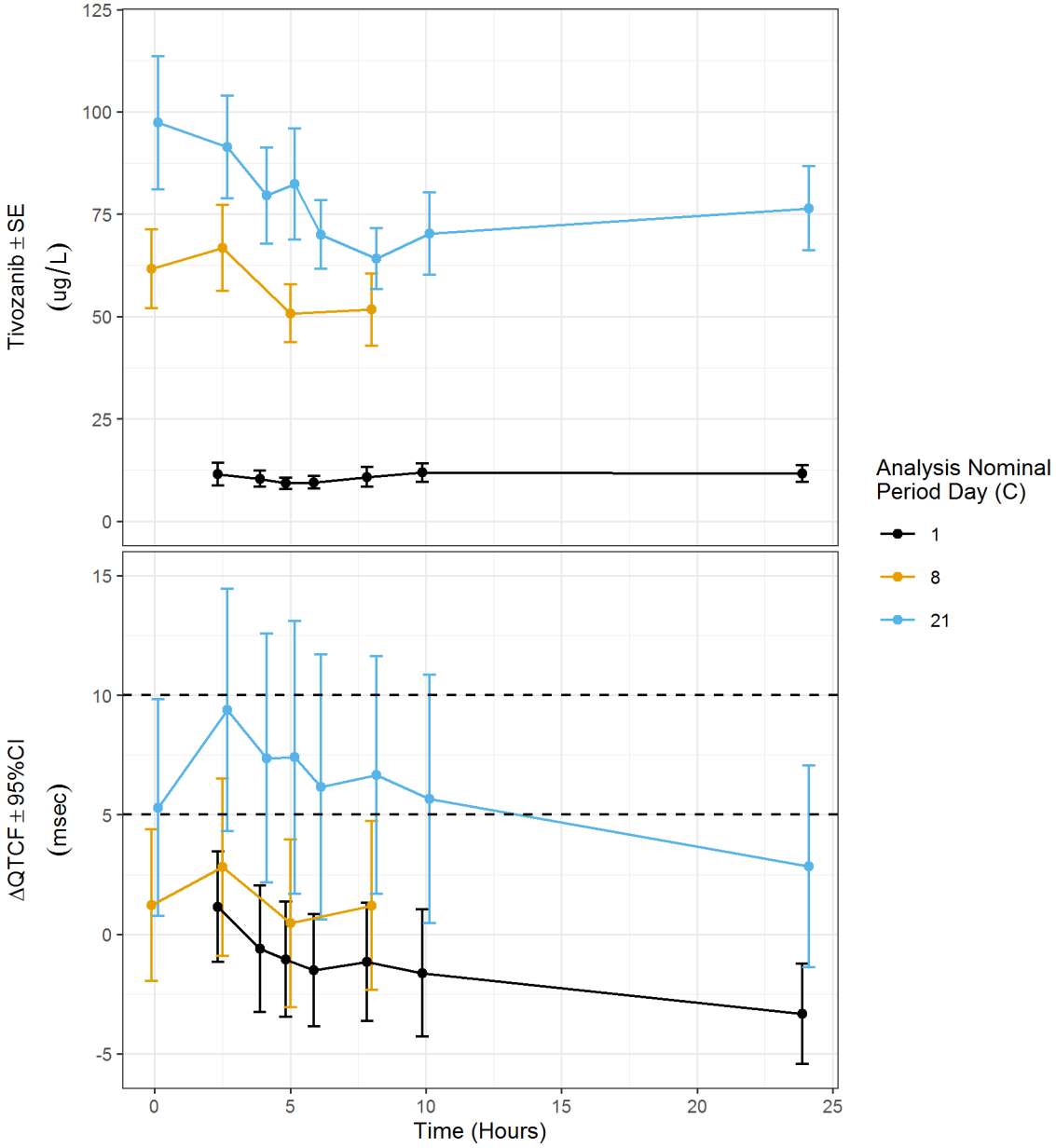
No subject had QRS >120 msec with 25% increase over baseline in the study.

4.5 EXPOSURE-RESPONSE ANALYSIS

The objective of the clinical pharmacology analysis was to assess the relationship between serum concentration of tivozanib and ΔQTcF. Exposure-response analysis was conducted using all subjects with baseline and at a least one post-baseline ECG with time-matched PK (Study # AV-951-10-112). Prior to evaluating the relationship between tivozanib concentration and QTc using a linear model, the three key assumptions of the model were evaluated using exploratory analysis: 1) absence of significant changes in heart rate (more than a 10 bpm increase or decrease in mean HR); 2) delay between tivozanib concentration and ΔQTc and 3) presence of non-linear relationship.

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Figure 5: Time course of tivozanib concentration (top) and QTc (bottom)



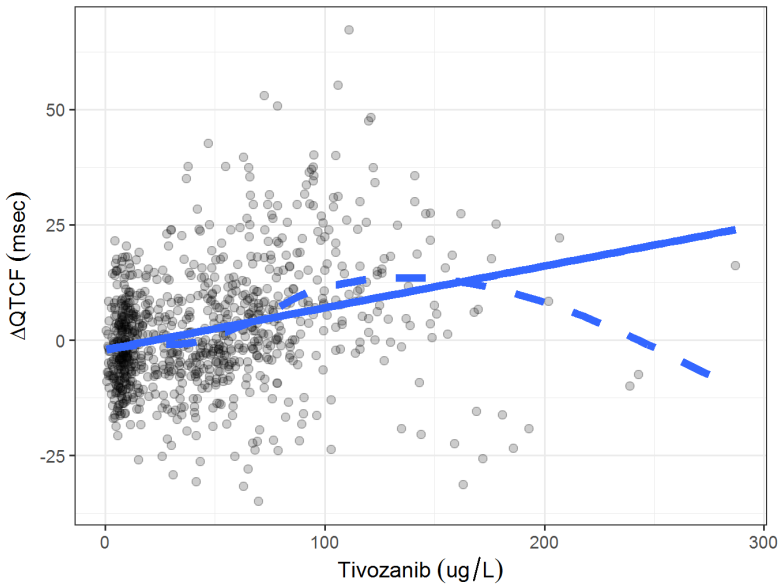
An evaluation of the time-course of tivozanib concentration and changes in ΔQTcF is shown in Figure 5. There was significant accumulation in tivozanib concentration following repeated dosing (Cmax: Day: ~15 ng/mL to Day 21: ~100 ng/mL). There was no apparent correlation between the time at maximum effect on ΔQTcF and peak concentrations of tivozanib indicating no significant hysteresis. Figure 2 shows the time-course of ΔΔHR, which shows an absence of significant ΔΔHR changes and the maximum change in heart rate is below 4 bpm (Sections 4.3.2 and 4.4.2).

After confirming the absence of significant heart rate changes or delayed QTc changes, the relationship between tivozanib concentration and ΔQTcF was evaluated to determine if a linear model would be appropriate. Figure 6 shows the relationship between tivozanib

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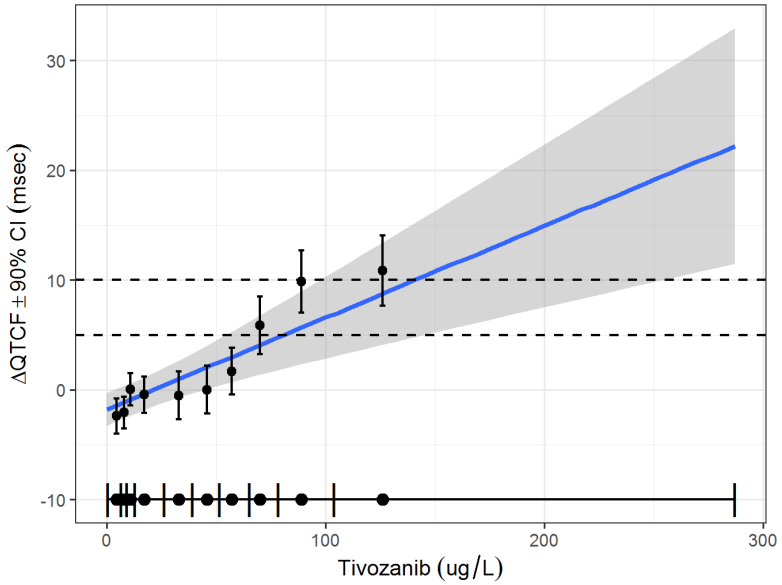
concentration and ΔQTc and supports the use of a linear model. There was limited data available above 200 ng/mL concentration.

Figure 6: Assessment of linearity of concentration-QTc relationship



Finally, the linear model was applied to the data and the goodness-of-fit plot is shown in Figure 7. Predictions from the concentration-QTc model are provided in Table 1.

Figure 7: Goodness-of-fit plot for QTc



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LABEL AND LABELING REVIEW
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	August 3, 2020
Requesting Office or Division:	Division of Oncology 1 (DO1)
Application Type and Number:	NDA 212904
Product Name, Dosage Form, and Strength:	Fotivda (tivozanib) capsules, 0.89 mg and 1.34 mg
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Aveo Pharmaceuticals, Inc.
FDA Received Date:	June 4, 2020 and July 29, 2020
OSE RCM #:	2020-662
DMEPA Safety Evaluator:	Tingting Gao, PharmD
DMEPA Team Leader (Acting):	Ashleigh Lowery, PharmD, BCCCP

Reference ID: 4650667

1 REASON FOR REVIEW

As part of the review process for Fotivda (tivozanib) capsules, the Division of Oncology 1 (DO1) requested that we review the proposed Fotivda prescribing information, patient information, and container labels for areas of vulnerability that may lead to medication errors.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B – N/A
Human Factors Study	C – N/A
ISMP Newsletters*	D – N/A
FDA Adverse Event Reporting System (FAERS)*	E – N/A
Other	F – N/A
Labels and Labeling	G

N/A=not applicable for this review
*We do not typically search FAERS or ISMP Newsletters for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

We reviewed the proposed Fotivda container labels, PI, and patient information and determined that the proposed Fotivda container labels and PI may be improved to ensure safe product use.

4 CONCLUSION & RECOMMENDATIONS

The proposed Fotivda container labels and PI may be improved to ensure safe product use. We provide specific recommendations in Section 4.1 and 4.2 below.

4.1 RECOMMENDATIONS FOR DIVISION OF ONCOLOGY 1 (DO1)

A. Prescribing Information

1. Dosage and Administration Section

a. Consider revising the dosage statement from "The recommended dosage of FOTIVDA is one 1.38 mg capsule taken orally once daily with or without food for 21 days on treatment followed by 7 days off treatment for a 28-day cycle." to "The recommended dosage of FOTIVDA is 1.38 mg taken orally once daily for 21 days on treatment followed by 7 days off treatment for a 28-day cycle." to clearly state the dose as "1.38 mg" instead of as "one 1.38 mg capsule". We also recommend separating the instruction to take Fotivda with or without food as a separate sentence to reduce clutter.

b. Since Patient Information includes the instruction "Swallow the FOTIVDA capsule whole with a glass of water. Do not open the capsule.", we recommend include this information in Dosage and Administration section of the PI.

4.2 RECOMMENDATIONS FOR AVEO PHARMACEUTICALS, INC.

We recommend the following be implemented prior to approval of this NDA:

A. Container Labels

1. The established name for drug products should include the finished dosage form, and the finished dosage form should appear on the same line as the active ingredient. If space does not permit the finished dosage form to appear on the same line as the active ingredient, we recommend placing the finished dosage form on the next line below the active ingredient. Therefore, revise the principal display panel so that it reads:

   Fotivda
   (tivozanib) capsules

2. Revise the statement "Dosage: see accompanying prescribing information" to read, "Recommended Dosage: See Prescribing Information."

3. As currently presented, the product codes *(middle 3 digits)* in the NDC number are sequential between the strengths. The middle digits are traditionally used by healthcare providers to check the correct product, strength, and formulation. Therefore, assignment of sequential numbers for the middle digits is not an effective differentiating feature (e.g., -100- and -101-). Revise the product code in the NDC numbers to ensure that the middle digits (-100- and -101-) are not sequential between the strengths. See *Draft Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors*, which, when finalized will represent the Agency's current

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thinking on the topics therein. Available from: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/safety-considerations-container-labels-and-carton-labeling-design-minimize-medication-errors.

4. To minimize confusion and reduce the risk for deteriorated drug medication errors, FDA recommends that the human-readable expiration date on the drug package label include a year, month, and non-zero day. FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a hyphen or forward slash to separate the portions of the expiration date. See *Draft Guidance for Industry: Product Identifiers under the Drug Supply Chain Security Act - Questions and Answers*, which, when finalized will represent the Agency's current thinking on the topics therein. Available from: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/product-identifiers-under-drug-supply-chain-security-act-questions-and-answers.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Fotivda received on June 17, 2020 from Aveo Pharmaceuticals, Inc..

Table 2. Relevant Product Information for Fotivda	
Initial Approval Date	N/A
Active Ingredient	tivozanib
Indication	the treatment of patients with relapsed or refractory renal cell carcinoma (RCC)
Route of Administration	oral
Dosage Form	capsules
Strength	0.89 mg and 1.34 mg
Dose and Frequency	1.34 mg once daily for 21 days followed by 7 days off treatment (28-day cycle). For patients with moderate hepatic impairment, take 0.89 mg once daily with or without food for 21 days on treatment followed by 7 days off treatment (28-day cycle).
How Supplied	Bottle of 21 capsules
Storage	Store at 20°C to 25°C (68°F to 77°F)
Container Closure	high-density polyethylene bottle with a (b) (4) cap.

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[a] along with postmarket medication error data, we reviewed the following Fotivda labels and labeling submitted by Aveo Pharmaceuticals, Inc..

- Container labels received on June 4, 2020
- Prescribing Information (Image not shown) received on June 17, 2020, available from \\cdsesub1\evsprod\nda212904\0010\m1\us\draft-labeling-text.doc
- Patient Information received onJune 17, 2020, available from \\cdsesub1\evsprod\nda212904\0010\m1\us\patient-information.doc

G.2 Label and Labeling Images

Container labels

(b) (4)



[a] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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