

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**212904Orig1s000**

**MULTI-DISCIPLINE REVIEW**

**Summary Review**

**Office Director**

**Cross Discipline Team Leader Review**

**Clinical Review**

**Non-Clinical Review**

**Statistical Review**

**Clinical Pharmacology Review**

### NDA/BLA Multi-Disciplinary Review and Evaluation

|                                                                                          |                                                                                                                                                                          |
|------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Application Type</b>                                                                  | New Molecular Entity and original NDA                                                                                                                                    |
| <b>Application Number(s)</b>                                                             | 212904                                                                                                                                                                   |
| <b>Priority or Standard</b>                                                              | Standard                                                                                                                                                                 |
| <b>Submit Date(s)</b>                                                                    | March 31, 2020                                                                                                                                                           |
| <b>Received Date(s)</b>                                                                  | March 31, 2020                                                                                                                                                           |
| <b>PDUFA Goal Date</b>                                                                   | March 31, 2021                                                                                                                                                           |
| <b>Division/Office</b>                                                                   | Division of Oncology 1/Office of Oncologic Diseases                                                                                                                      |
| <b>Review Completion Date</b>                                                            | Electronic stamp date                                                                                                                                                    |
| <b>Established/Proper Name</b>                                                           | Tivozanib                                                                                                                                                                |
| <b>(Proposed) Trade Name</b>                                                             | FOTIVDA®                                                                                                                                                                 |
| <b>Pharmacologic Class</b>                                                               | kinase inhibitor                                                                                                                                                         |
| <b>Code name</b>                                                                         | AV-951                                                                                                                                                                   |
| <b>Applicant</b>                                                                         | AVEO Pharmaceuticals, Inc                                                                                                                                                |
| <b>Doseage form</b>                                                                      | capsule                                                                                                                                                                  |
| <b>Applicant proposed Dosing Regimen</b>                                                 | 1.34 mg once daily with or without food for 21 days on treatment followed by 7 days off treatment (28-day cycle)                                                         |
| <b>Applicant Proposed Indication(s)/Population(s)</b>                                    | FOTIVDA is indicated for the treatment of patients with relapsed or refractory renal cell carcinoma.                                                                     |
| <b>Applicant Proposed SNOMED CT Indication Disease Term for each Proposed Indication</b> | 702391001: Renal cell carcinoma (disorder)                                                                                                                               |
| <b>Recommendation on Regulatory Action</b>                                               | Regular Approval                                                                                                                                                         |
| <b>Recommended Indication(s)/Population(s) (if applicable)</b>                           | FOTIVDA is indicated for the treatment of adult patients with relapsed or refractory advanced renal cell carcinoma (RCC) following two or more prior systemic therapies. |
| <b>Recommended SNOMED CT Indication Disease Term for each Indication (if applicable)</b> | 702391001: Renal cell carcinoma (disorder)                                                                                                                               |
| <b>Recommended Dosing Regimen</b>                                                        | 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      |

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## Reviewers of Multi-Disciplinary Review and Evaluation

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|                                         |                                                                                                                                                                                                               |
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|                  |                                                     |
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OPQ=Office of Pharmaceutical Quality  
 OPDP=Office of Prescription Drug Promotion  
 OSI=Office of Scientific Investigations  
 OSE= Office of Surveillance and Epidemiology  
 DEPI= Division of Epidemiology  
 DMEPA=Division of Medication Error Prevention and Analysis  
 DRM=Division of Risk Management

## Glossary

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|         |                                                        |
|---------|--------------------------------------------------------|
| AC      | advisory committee                                     |
| ADME    | absorption, distribution, metabolism, excretion        |
| AE      | adverse event                                          |
| AR      | adverse reaction                                       |
| BIRC    | blinded independent radiology review committee         |
| BLA     | biologics license application                          |
| BPCA    | Best Pharmaceuticals for Children Act                  |
| BRF     | Benefit Risk Framework                                 |
| CBER    | Center for Biologics Evaluation and Research           |
| CDER    | Center for Drug Evaluation and Research                |
| CDRH    | Center for Devices and Radiological Health             |
| CDTL    | Cross-Discipline Team Leader                           |
| CFR     | Code of Federal Regulations                            |
| CMC     | chemistry, manufacturing, and controls                 |
| COSTART | Coding Symbols for Thesaurus of Adverse Reaction Terms |
| CPI     | checkpoint inhibitor                                   |
| CRF     | case report form                                       |
| CRO     | contract research organization                         |
| CRT     | clinical review template                               |
| CSR     | clinical study report                                  |
| CSS     | Controlled Substance Staff                             |
| dBp     | diastolic blood pressure                               |
| DHOT    | Division of Hematology Oncology Toxicology             |
| DMC     | data monitoring committee                              |
| DRISK   | Division of Risk Management                            |
| ECG     | electrocardiogram                                      |
| eCTD    | electronic common technical document                   |
| ETASU   | elements to assure safe use                            |
| FDA     | Food and Drug Administration                           |
| FDAAA   | Food and Drug Administration Amendments Act of 2007    |
| FDASIA  | Food and Drug Administration Safety and Innovation Act |
| GCP     | good clinical practice                                 |
| GRMP    | good review management practice                        |
| HR      | hazard ratio                                           |
| ICH     | International Conference on Harmonisation              |
| IMDC    | International Metastatic RCC Database Consortium       |
| IND     | Investigational New Drug                               |
| IR      | Information Request                                    |
| ISE     | integrated summary of effectiveness                    |
| ISS     | integrated summary of safety                           |

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|           |                                                                         |
|-----------|-------------------------------------------------------------------------|
| ITT       | intent to treat                                                         |
| KI        | kinase inhibitor                                                        |
| MedDRA    | Medical Dictionary for Regulatory Activities                            |
| mITT      | modified intent to treat                                                |
| mTOR      | mammalian target of rapamycin                                           |
| NCI-CTCAE | National Cancer Institute-Common Terminology Criteria for Adverse Event |
| NDA       | new drug application                                                    |
| NME       | new molecular entity                                                    |
| OCS       | Office of Computational Science                                         |
| ODAC      | Oncologic Drugs Advisory Committee                                      |
| OOD       | Office of Oncologic Diseases                                            |
| OPQ       | Office of Pharmaceutical Quality                                        |
| ORR       | objective response rate                                                 |
| OS        | overall survival                                                        |
| OSE       | Office of Surveillance and Epidemiology                                 |
| OSI       | Office of Scientific Investigation                                      |
| PBRER     | Periodic Benefit-Risk Evaluation Report                                 |
| PD        | pharmacodynamics                                                        |
| PD-1      | programmed death - 1                                                    |
| PD-L1     | programmed death ligand -1                                              |
| PFS       | progression-free survival                                               |
| PI        | prescribing information                                                 |
| PK        | pharmacokinetics                                                        |
| PMC       | postmarketing commitment                                                |
| PMR       | postmarketing requirement                                               |
| PP        | per protocol                                                            |
| PPI       | patient package insert (also known as Patient Information)              |
| PREA      | Pediatric Research Equity Act                                           |
| PRO       | patient reported outcome                                                |
| PSUR      | Periodic Safety Update report                                           |
| QD        | daily                                                                   |
| RECIST    | Response Evaluation Criteria in Solid Tumors                            |
| REMS      | risk evaluation and mitigation strategy                                 |
| SAE       | serious adverse event                                                   |
| TKI       | tyrosine kinase inhibitor                                               |
| sBP       | systolic blood pressure                                                 |
| SAP       | statistical analysis plan                                               |
| SGE       | special government employee                                             |
| SOC       | standard of care                                                        |
| TEAE      | treatment emergent adverse event                                        |
| VEGFR     | vascular endothelial growth factor receptor                             |

## 1 Executive Summary

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### 1.1. Product Introduction

Tivozanib is a kinase inhibitor (KI) that inhibits phosphorylation of vascular endothelial growth factor receptor (VEGFR) 1, VEGFR 2 and VEGFR 3 and inhibits other kinases including c-kit and PDGFR  $\beta$  at clinically relevant concentrations, as demonstrated via in vitro cellular kinase assays.

The proposed dosing schedule is 1.34 mg taken orally once daily for 21 days on treatment followed by 7 days off treatment for a 28-day cycle until disease progression or unacceptable toxicity.

Tivozanib is a new molecular entity that was not approved in the U.S. for any indication at the time of submission of this application.

### 1.2. Conclusions on the Substantial Evidence of Effectiveness

The review team recommends approval of tivozanib, according to 21 Code of Federal Regulations (CFR), Part 314.50, Subpart B, for the following indication:

“FOTIVDA is indicated for the treatment of adult patients with relapsed or refractory advanced renal cell carcinoma (RCC) following two or more prior systemic therapies”

The basis for the recommendation is a favorable benefit-risk profile for tivozanib in patients with advanced RCC. In a Phase 3 trial, TIVO-3, 350 patients with advanced renal cell carcinoma were randomized in a 1:1 ratio to tivozanib at a dose of 1.34 mg once daily for 21 consecutive days followed by 7 days off or to sorafenib 400 mg twice daily. Randomization was stratified by International Metastatic RCC Database Consortium (IMDC) risk category and prior therapy (2 prior tyrosine kinase inhibitor (TKI) vs. 1 prior TKI + prior checkpoint inhibitors (CPI) vs. 1 prior TKI + any other agent). To be eligible, patients were required to have had previous treatment with 2 prior lines of systemic therapy and to have an ECOG PS  $\leq 1$ . Baseline characteristics were balanced between arms on TIVO-3; approximately half of patients on both arms received 2 prior TKIs, approximately one quarter of patients on both arms received 1 prior TKI + prior CPI, and approximately one quarter of patients on both arms received 1 prior TKI and another systemic agent.

The major efficacy outcome measure was progression free survival (PFS) in all randomized patients per Blinded Independent Review Committee (BIRC) review of imaging. A statistically significant improvement in PFS was observed for patients randomized to tivozanib (n=175) vs. sorafenib (n=175). The estimate of the hazard ratio (HR) for PFS was 0.73 (95% CI: 0.56 to 0.95, p-value of 0.016). Median PFS estimate was 5.59 months (95% CI: 4.83, 7.33) in the tivozanib

arm vs. 3.88 months (95% CI: 3.71 to 5.55) in the sorafenib arm. Consistent results were observed across the pre-specified subgroups. The final median overall survival (OS) estimate was 16.39 months for the tivozanib arm vs. 19.15 months for the sorafenib arm; however, the HR was 0.97 (95% CI: 0.75 to 1.24). The objective response rate (ORR) was 18% (95% CI: 12%, 24%) in the tivozanib arm vs. 8% (95% CI: 4%, 13%) in the sorafenib arm; these results were supportive of the overall efficacy of tivozanib vs. sorafenib.

Progression-free survival is considered by FDA to be an acceptable endpoint to demonstrate the effectiveness of new therapeutics across many oncology indications and has been the primary basis for approval of therapies indicated for the treatment of advanced renal cell carcinoma. Although the overall difference in median PFS between arms was 1.71 months, which is shorter than the 8 week scanning interval on the trial, a post-hoc interval censoring analysis conducted by FDA to explore the robustness of these results with respect to the imaging assessment interval was consistent with the primary analysis. Because the study was a replacement trial design compared to standard of care therapy, the benefit in PFS was deemed appropriate to support substantial evidence of effectiveness.

The OS HR estimate was >1 favoring sorafenib [i.e. HR of 1.12 (0.4-1.51)] at an interim analysis of OS and thus FDA recommended further follow up. The final OS analysis showed a HR of 0.97 (95% CI: 0.75 to 1.24), which reflected a more mature timepoint in the overall survival curve than the earlier analysis. The estimate of median OS was longer on the sorafenib arm, but the median OS is thought to represent only one timepoint on the survival curve and not the overall curve. With that, the FDA conducted a post-hoc exploratory analysis in which the restricted mean survival time (RMST) difference between the two arms was calculated using different cutoff timepoints. Considering the small difference observed between the two treatment arms in the RMST analysis, together with the overlapped survival curves and the HR estimate of 0.97 in favor of the tivozanib arm, the review team concluded that overall, no decrement in overall survival was observed for patients on the tivozanib arm.

The PFS and OS results were also interpreted in the setting of an active control arm of sorafenib, which had previously demonstrated a PFS and OS advantage in patients with advanced renal cell carcinoma compared to placebo. Any efficacy observed in the tivozanib arm in terms of a PFS advantage was thus considered additive to the effect that sorafenib had on its own in this setting. Consistent efficacy was also demonstrated in the ~25% of patients who were pretreated with a CPI, which would be more similar to a contemporary US population in the later-line setting with the recent approval of multiple CPI-containing combinations in the first-line metastatic setting.

The safety profile of tivozanib was considered within range for this patient population and was similar to that observed with other kinase inhibitors. For patients receiving tivozanib on TIVO-3, deaths due to TEAEs occurred in 7.5% including pneumonia, hepatobiliary disorders, respiratory failure, myocardial infarction, cerebrovascular accident, and subdural hematoma. Grade 3-4 TEAEs occurred in 67%, and treatment discontinuations occurred in 21%. The most common TEAEs observed for patients on the tivozanib arm included fatigue, hypertension, diarrhea,

decreased appetite, nausea, dysphonia, hypothyroidism, cough, and stomatitis. Hypertension and hypertensive crisis, cardiac failure, cardiac ischemia and arterial thromboembolic events, venous thromboembolic events, hemorrhagic events, proteinuria, thyroid dysfunction, risk of impaired wound healing, reversible posterior leukoencephalopathy syndrome, embryo-fetal toxicity, and allergic reactions to tartrazine are included as Warnings and Precautions in the tivozanob labeling.

Overall, patients receiving tivozanib on TIVO-3 had lower rates of dose reduction, interruption, or permanent discontinuation than those receiving sorafenib. Although no Patient-Reported Outcome data (PROs) were collected on TIVO-3, analysis of PROs from TIVO-1 which also randomized patients with advanced RCC to tivozanib vs sorafenib (in the first-line setting) suggested an improvement in the analysis of overall treatment bother results. This suggests an overall improved tolerability over an accepted standard-of-care according to several clinically relevant metrics. The safety profile of tivozanib was further supported by review of safety data from an additional 835 patients in other clinical trials who received the dose of tivozanib under current review.

Tivozanib had previously been evaluated in TIVO-1, which randomized patients with treatment-naïve advanced RCC to receive tivozanib versus sorafenib. Although TIVO-1 met its primary endpoint (PFS HR = 0.80 [95% CI: 0.64, 0.99],  $p = 0.04$ ), a trend towards a detrimental effect on survival was observed with tivozanib (OS HR = 1.25 [95% CI: 0.95, 1.62],  $p = 0.11$ ). The FDA team convened a meeting of the Oncologic Drug Advisory Committee (ODAC) on May 2, 2013 to discuss this application. The Applicant presented their perspective that the reason for the overall survival results was the one-way crossover aspect of the study design. However, ODAC voted 13:1, "No," in response to the question "Has the Applicant demonstrated a favorable benefit to risk evaluation for the treatment of renal cell carcinoma in an adequate and well-controlled trial?", citing concerns that included the observed decrement in the HR estimate for OS and confounding factors in the trial design.

Despite the negative previous ODAC vote for tivozanib and the subsequent CR letter issued on June 6, 2013 for tivozanib based on review of TIVO-1, the review team felt that the totality of the TIVO-3 data warranted an approval in this case given the PFS advantage, supportive ORR, detailed safety analysis, and the HR for OS that ultimately did not demonstrate a decrement in patients who were required to have had previous treatment with 2 prior lines of therapy. Although the Applicant had requested an indication that included all patients with advanced renal cell carcinoma, the FDA review team granted an indication that reflected the TIVO-3 enrolled population and not the TIVO-1 population, i.e. patients who progressed on two prior lines of therapy.

Labeling was drafted with the input and the agreement of all discipline-specific review teams and the Applicant. All disciplines were in favor of a regular approval. There are no postmarketing requirements or postmarketing commitments for this application.

### 1.3. **Benefit-Risk Assessment**

#### **Benefit-Risk Summary and Assessment**

Patients with relapsed or refractory advanced renal cell carcinoma following two or more prior systemic therapies may receive a TKI (different than one received previously) or an mTOR inhibitor on progression; however there is no therapy specifically approved in this line of treatment. Thus patients with advanced RCC who progressed on two prior lines of therapy, including a TKI, were evaluated in TIVO-3, which randomized 350 patients to tivozanib or sorafenib with a primary endpoint of PFS per BIRC assessment.

The primary efficacy analysis for TIVO-3 demonstrated a PFS benefit per BIRC assessment for treatment with tivozanib (n=175) vs. sorafenib (n=175). The estimate of the hazard ratio for PFS was 0.73 (95% CI: 0.56 to 0.95, p-value of 0.016). Median PFS estimate was 5.59 months (95% CI: 4.83, 7.33) in the tivozanib arm vs. 3.88 months (95% CI: 3.71 to 5.55) in the sorafenib arm. Subgroup analyses were consistent across the prespecified stratification factors of IMDC risk category and prior therapy (2 prior TKIs vs. 1 prior TKI + prior CPI vs. 1 prior TKI + any other agent). The final median OS estimate was 16.39 months for the tivozanib arm vs. 19.15 months for the sorafenib arm, with a HR of 0.97 (95% CI: 0.75 to 1.24) for tivozanib. The ORR was 18% (95% CI: 12%, 24%) in the tivozanib arm vs. 8% (95% CI: 4%, 13%) in the sorafenib arm; these results were supportive of the overall efficacy of tivozanib vs. sorafenib.

The safety profile of tivozanib for patients on TIVO-3 was in line with the known safety profile described with other TKIs. Deaths due to an adverse event (excluding disease progression) occurred in 7.5% of tivozanib-treated patients on TIVO-3 and included pneumonia, hepatobiliary disorders, respiratory failure, myocardial infarction, cerebrovascular accident, and subdural hematoma. Permanent treatment discontinuation due to adverse events occurred in 21%. Grade 3-4 adverse events occurred in 67% of patients and the most common (>20%) all-grade adverse events were fatigue, hypertension, diarrhea, decreased appetite, nausea, dysphonia, hypothyroidism, cough, and stomatitis. Warnings and Precautions for tivozanib include hypertension and hypertensive crisis, cardiac failure, cardiac ischemia and arterial thromboembolic events, venous thromboembolic events, hemorrhagic events, proteinuria, thyroid dysfunction, risk of impaired wound healing, reversible posterior leukoencephalopathy syndrome, embryo-fetal toxicity, and allergic reactions to tartrazine.

According to 21 CFR, Part 314.50, Subpart B a regular approval for tivozanib is recommended. All review disciplines are in agreement.

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| Dimension                                 | Evidence and Uncertainties                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | Conclusions and Reasons                                                                                                                                                                                                                                                                                                                        |
|-------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <a href="#">Analysis of Condition</a>     | <ul style="list-style-type: none"> <li>Patients with advanced RCC whose disease has progressed on two prior lines of therapy represent a group of patients with an unmet medical need whose disease is considered incurable.</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | <p><b>Advanced RCC is a serious and life-threatening condition</b></p>                                                                                                                                                                                                                                                                         |
| <a href="#">Current Treatment Options</a> | <ul style="list-style-type: none"> <li>There is no therapy specifically approved in the 3rd line of treatment, however there are several approved TKIs for the treatment of advanced RCC which are active and can be used in the third-line setting (including sorafenib).</li> <li>Combination therapies which include CPIs are approved in the first-line setting, and in the case of nivolumab, in the second-line setting. Most patients have therefore been treated and have progressed or are intolerant to these therapies by the time they have reached the later lines of therapy.</li> <li>Other treatment options for patients with advanced RCC in the later lines include mTOR inhibitors and bevacizumab, although these are used infrequently.</li> </ul> | <p><b>Although treatment options exist, none are curative and none is approved specifically for patients whose disease has progressed after treatment with 2 prior lines of therapy. Therefore, there is an unmet medical need for new effective treatments for patients with advanced RCC who have received 2 prior lines of therapy.</b></p> |
| <a href="#">Benefit</a>                   | <ul style="list-style-type: none"> <li>In the analysis of TIVO-3, the estimate for the HR for PFS was 0.73 (95% CI: 0.56 to 0.95, p-value of 0.016). Median PFS estimate was 5.59 months (95% CI: 4.83, 7.33) in the tivozanib arm vs. 3.88 months (95% CI: 3.71 to 5.55) in the sorafenib arm. Subgroup analyses were supportive.</li> <li>ORR was 18% (95% CI: 12%, 24%) in the tivozanib arm vs. 8% (95% CI: 4%, 13%) in the sorafenib arm.</li> <li>The final median OS estimate was 16.39 months for the tivozanib arm vs. 19.15 months for the sorafenib arm, with a HR estimate of 0.97 (95% CI: 0.75 to 1.24).</li> </ul>                                                                                                                                        | <p><b>Tivozanib has demonstrated a PFS advantage over sorafenib in patients with advanced RCC whose disease has progressed after treatment with 2 prior lines of therapy. The submitted evidence meets the statutory evidentiary standard for regular approval of tivozanib for this indication.</b></p>                                       |

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| Dimension                                | Evidence and Uncertainties                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | Conclusions and Reasons                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
|------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <a href="#">Risk and Risk Management</a> | <ul style="list-style-type: none"> <li>• The safety profile of tivozanib was similar to the known safety profile for TKIs.</li> <li>• When compared to patients on the sorafenib arm of TIVO-3, patients on the tivozanib arm had lower rates of dose reduction, interruption, or permanent discontinuation.</li> <li>• Although no PROs were collected on TIVO-3, analysis of PROs from TIVO-1 suggested an improvement in the analysis of overall treatment bother results. These metrics suggest an overall improved tolerability over sorafenib which is an accepted standard-of-care.</li> </ul> | <p><b>The safety profile of tivozanib is acceptable in this advanced setting and is manageable with dose modifications and supportive care as needed.</b></p> <p><b>The significant and potentially serious adverse reactions of tivozanib are adequately addressed in the Warnings and Precautions section and the dose modification recommendations included in product labeling.</b></p> <p><b>There were no safety concerns identified during NDA review requiring risk management beyond labeling or warranting consideration for Risk Evaluation and Mitigation Strategy (REMS).</b></p> |

#### 1.4. Patient Experience Data

##### Patient Experience Data Relevant to this Application (check all that apply)

|                                     |                                                                                                                                    |                                                                                      |
|-------------------------------------|------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------|
| <input type="checkbox"/>            | <b>The patient experience data that were submitted as part of the application include:</b>                                         | Section of review where discussed, if applicable [e.g., Section 6.1 Study endpoints] |
| <input type="checkbox"/>            | Clinical outcome assessment (COA) data, such as                                                                                    |                                                                                      |
| <input type="checkbox"/>            | Patient reported outcome (PRO)                                                                                                     |                                                                                      |
| <input type="checkbox"/>            | Observer reported outcome (ObsRO)                                                                                                  |                                                                                      |
| <input type="checkbox"/>            | Clinician reported outcome (ClinRO)                                                                                                |                                                                                      |
| <input type="checkbox"/>            | Performance outcome (PerFO)                                                                                                        |                                                                                      |
| <input type="checkbox"/>            | Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.) |                                                                                      |
| <input type="checkbox"/>            | Patient-focused drug development or other stakeholder meeting summary reports                                                      |                                                                                      |
| <input type="checkbox"/>            | Observational survey studies designed to capture patient experience data                                                           |                                                                                      |
| <input type="checkbox"/>            | Natural history studies                                                                                                            |                                                                                      |
| <input type="checkbox"/>            | Patient preference studies (e.g., submitted studies or scientific publications)                                                    |                                                                                      |
| X                                   | Other: (Please specify): PROs from another trial (TIVO-1)                                                                          |                                                                                      |
| <input checked="" type="checkbox"/> | <b>Patient experience data that were not submitted in the application, but were considered in this review:</b>                     |                                                                                      |
| <input type="checkbox"/>            | Input informed from participation in meetings with patient stakeholders                                                            |                                                                                      |
| <input type="checkbox"/>            | Patient-focused drug development or other stakeholder meeting summary reports                                                      |                                                                                      |
| <input type="checkbox"/>            | Observational survey studies designed to capture patient experience data                                                           |                                                                                      |
| <input checked="" type="checkbox"/> | Other: (Please specify): PRO results from another trial (TIVO-1, from NDA 204408)                                                  | Section 8.2.6                                                                        |
| <input type="checkbox"/>            | <b>Patient experience data was not submitted as part of this application.</b>                                                      |                                                                                      |

X

Chana Weinstock, MD  
 Cross Discipline Team Leader

## 2 Therapeutic Context

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### 2.1. Analysis of Condition

Renal cell carcinoma (RCC) is a serious and life-threatening condition. In 2021, an estimated 76,080 new diagnoses of kidney cancer will be made and 13,780 deaths will occur in the U.S.[1] Approximately 80-90% of kidney cancers are RCC, and 16% of kidney cancers are metastatic at diagnosis. Kidney cancer deaths comprise 2.4% of cancer deaths in the U.S. The 5-year survival of newly diagnosed metastatic kidney cancer is 13%.[2] Clear cell RCC is the most common histologic subtype in adults, comprising approximately 80% of RCC cases.[3]

### 2.2. Analysis of Current Treatment Options

Advanced RCC is a malignancy that was historically difficult to treat with systemic therapy due to its chemoresistant nature. The approval of sorafenib and sunitinib in 2005 and 2006 offered patients the first kinase inhibitors for advanced RCC. This was followed by subsequent approval of other kinase inhibitors for treatment of patients with advanced RCC including pazopanib, axitinib, cabozantinib, and lenvatinib, and kinase inhibitors have become a mainstay of treatment for patients with advanced RCC.

Other treatment options available in the U.S., although used less frequently, include bevacizumab, a monoclonal antibody against VEGFR, and mammalian target of rapamycin (mTOR) inhibitors such as everolimus.

Nivolumab was the first CPI approved for the second line treatment of advanced RCC in 2016. Since that time, the treatment landscape in RCC has continued to evolve with the approval of several CPI-containing combination regimens in frontline setting beginning in 2018. These combinations include nivolumab plus ipilimumab, pembrolizumab plus axitinib, avelumab plus axitinib, and nivolumab plus cabozantinib. The standard second-line therapy has not been established since these frontline approvals occurred. However, since there are multiple options for frontline therapy, guidelines generally suggest considering any one of a number of regimens as reasonable choices, including any of the frontline options to which the patient has not been exposed, as well as kinase inhibitors that could be used as monotherapy or in combination. These include cabozantinib with or without nivolumab, nivolumab with or without ipilimumab, axitinib with or without avelumab, and lenvatinib with everolimus.

There is currently no therapy specifically approved in the third-line setting for treatment of advanced RCC, however several KIs have a line-agnostic approval for treatment of advanced RCC.

#### **Table 1. Summary of Kinase Inhibitors (KI) Approved for Advanced RCC**

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| Drug (year granted approval)     | Comparator   | Primary endpoint | PFS HR (95% CI)      | OS HR (95% CI)                     | Indication granted |
|----------------------------------|--------------|------------------|----------------------|------------------------------------|--------------------|
| Sorafenib (2005)[4, 5]           | Placebo      | PFS              | 0.44<br>(0.35, 0.55) | 0.72<br>(0.55, 0.95)               | Line-agnostic      |
| Sunitinib <sup>1</sup> (2006)[6] | N/A          | ORR              | N/A                  | N/A                                | Line-agnostic      |
| Sunitinib (2007)[7]              | IFN $\alpha$ | PFS              | 0.42<br>(0.32, 0.54) | 0.82<br>(0.67, 1.001) <sup>3</sup> | Line-agnostic      |
| Pazopanib (2009)[8]              | Placebo      | PFS              | 0.46<br>(0.34, 0.62) | 0.91<br>(0.71-1.16) <sup>4</sup>   | Line-agnostic      |
| Axitinib (2012)[10]              | Sorafenib    | PFS              | 0.67<br>(0.54, 0.81) | 0.97<br>(0.80-1.17)                | Second-line        |
| Cabozantinib (2017)[11]          | Sunitinib    | PFS              | 0.48<br>(0.31, 0.74) | 0.80<br>(0.53, 1.21)               | Line-agnostic      |

<sup>1</sup>Accelerated approval.

<sup>2</sup>Regular approval.

<sup>3</sup>Per final OS analysis [12] because OS was not mature at time of approval.

<sup>4</sup>Per final OS analysis [13] because OS was not mature at time of approval.

**Table 2. Other KI vs. KI Trial Efficacy Results**

| Drug          | Comparator | Primary endpoint         | PFS HR (95% CI)      | OS HR (95% CI)        |
|---------------|------------|--------------------------|----------------------|-----------------------|
| Pazopanib [9] | Sunitinib  | PFS<br>(non-inferiority) | 1.05<br>(0.90, 1.22) | 0.91;<br>(0.76, 1.08) |
| Axitinib [15] | Sorafenib  | PFS                      | 0.77<br>(0.56, 1.05) | 0.995<br>(0.73-1.36)  |

### 3 Regulatory Background

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#### 3.1. U.S. Regulatory Actions and Marketing History

Tivozanib is not approved in the U.S. It has been approved by regulatory agencies in Europe (European Medicines Agency [EMA]) and New Zealand.

#### 3.2. Summary of Presubmission/Submission Regulatory Activity

**September 27, 2012** (NDA 204408): The Applicant submitted an NDA for tivozanib for the proposed indication of adults with unresectable or metastatic RCC based on the results of TIVO-1. TIVO-1 was a multicenter trial that randomized patients with KI-naïve advanced RCC to receive tivozanib versus sorafenib. See also Section 8.1.3.

The study met its primary endpoint (PFS HR = 0.80 [95% CI: 0.64, 0.99], p = 0.04). However, a trend towards a detrimental effect on survival with tivozanib (OS HR = 1.25 [95% CI: 0.95, 1.62], p = 0.11) was observed. Therefore, the FDA team decided to discuss the application at an Oncologic Drug Advisory Committee (ODAC).

**May 2, 2013:** An ODAC was convened to discuss TIVO-1 results and considerations for approval. The Applicant presented their perspective that the reason for the overall survival results was the one-way crossover aspect of the study design. ODAC voted 13:1, “No,” in response to the question “Has the Applicant demonstrated a favorable benefit to risk evaluation for the treatment of renal cell carcinoma in an adequate and well-controlled trial?” Committee members summarized the main concerns as being primarily a lack of confidence in the benefit-risk evaluation due to the decrement in the overall survival trend, trial design with confounding factors that limited interpretation of the results, and low enrollment from the U.S. that might impact the generalizability of results.[16]

**June 6, 2013:** FDA issued a Complete Response letter for NDA 204408. The letter cited one Clinical issue and one Product Quality issue:

Clinical Deficiency: The inconsistent PFS and OS results and imbalance in post study treatments make the trial’s results uninterpretable and inconclusive when making a risk-benefit assessment necessary for drug approval. FDA recommended that the sponsor perform an adequate and well-controlled randomized trial(s) of tivozanib using PFS as the primary endpoint and OS as a secondary endpoint. The sponsor should ensure the applicability of the results from this trial to the US population. The trial should be powered to detect a difference in PFS and adequately sized to reassure us that there is no adverse effect on OS. The design, conduct, and results of this trial will determine whether one additional trial will be sufficient for approval purposes.

Product Quality Deficiency: The 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 the NDA is

resubmitted, the sponsor was instructed to include the revised specifications table for the drug product with the updated dissolution acceptance criterion.

**May 2015** (IND 075547): A Pre-Phase 3 Meeting was held to obtain feedback on the design of a new multinational phase 3 study (TIVO-3) comparing tivozanib to sorafenib in the third-line setting for patients with advanced RCC who progressed on/after at least two regimens, including at least 1 VEGFR-TKIs (excluding sorafenib). The proposed design included: primary endpoint of PFS by independent radiological review; first secondary endpoint of OS; statistical plan to enroll 314 patients, assuming a PFS difference of two months (4 months vs. 6 months, HR 0.5); stratification factors of number of prior treatments (2 or  $\geq 2$ ) and number of metastatic sites/organs involved (1 or  $\geq 2$ ).

FDA agreed generally that the proposed study could support the proposed indication in the third-line setting. FDA's additional feedback was that the sponsor should provide justification for the statistical assumptions around PFS, should state assumptions for OS, and should justify the decision to allow patients to continue study therapy after receiving radiation therapy for progressive disease.

**November 6, 2015:** The sponsor submitted the statistical analysis plan (SAP) for TIVO-3, which stated that: "The interim OS analysis will be done at the time of the final PFS analysis. Assuming a median OS for sorafenib of 12 months and a median OS for tivozanib of 16 months, 245 OS events at the time of final OS analysis and 149 OS events at the time of final PFS analysis will yield approximately 61% power to demonstrate longer OS for tivozanib using the log-rank test, given 2.5% type I error (one-sided). The final OS analysis will be performed when all subjects have been lost to follow-up, have withdrawn consent, or have died, or when all subjects in follow-up have been on-study for at least 2 years, whichever occurs first."

**November 8, 2018:** The sponsor requested a Pre-NDA Meeting after conducting the first interim analysis (IA), which showed a statistically improved PFS with HR 0.73 (0.56, 0.94),  $p=0.0165$  and OS HR 1.12 (0.4-1.51) based on 183 OS events (70% information fraction).

**January 24, 2019:** Pre-NDA meeting. FDA's preliminary comments discouraged the sponsor from submitting an NDA at the time due to the overall survival results, which showed a trend towards a detriment in OS in both TIVO-1 and TIVO-3. The sponsor agreed to not submit an NDA. The sponsor stated that they were considering conducting a formal interim analysis at a later date with a Type I error allocation based on the percentage information.

**February 21, 2019:** The SAP version 4 submitted to FDA, where the final OS analysis was changed to the second IA, to be done when all patients had been on study for 2 years. An additional final OS analysis was added which would occur when 75% of patients would experience an event, at 263 OS events. See Table 5 in Section 8.1 for details.

**October 23, 2019:** Type B Pre-NDA meeting to discuss the second IA OS results: OS HR 0.99

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(0.76-1.29). The median overall survival for tivozanib was still worse than that of sorafenib (16.4 vs. 19.7 months). FDA stated: “Given the totality of evidence presented to date we recommend that you do not submit this application at this time.” The sponsor’s rationale was that TIVO-3 was the only trial to demonstrate a TKI with superior PFS over another in the post-immune checkpoint setting and that they were confident OS would not worsen with further follow-up. Thus, they proposed to submit the NDA in December 2019 as originally planned and submit the final OS in June 2020, during the review cycle. FDA recommended submitting an updated SAP with details of the final OS analysis based on the projected number of events at that time.

**November 2019:** SAP version 6 was submitted to FDA, where the timing of the final OS analysis was changed to a specific date rather than being event-driven.

“Simulations of OS projections (as of October 23, 2019) suggest that the additional number of OS events will not dramatically change the OS curve... The final OS analysis will occur on May 1, 2020 based on an estimate of approximately 4 OS events occurring per month (or approximately 263 OS events at that time)... At this analysis, 100% of the information fraction will be observed.”

**March 31, 2020:** NDA 212904 submitted to FDA.

## 4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

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### 4.1. Office of Scientific Investigations (OSI)

For TIVO-3, 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 patient 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 noncompliance. There was no evidence of harm to patients 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.

### 4.2. Product Quality

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: **A 60-month expiry dating period is granted for Fotivda® (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].**

The previous product quality deficiency identified in NDA 204408 was addressed adequately in the current submission. The applicant agreed to tighten the dissolution acceptance criterion to (b) (4) % at 20 minutes, which is found acceptable by the biopharmaceutics reviewer.

See the FDA Integrated Quality Review filed under this NDA on 2/17/2021 for complete details.

#### 4.1. Clinical Microbiology

N/A

#### 4.2. **Devices and Companion Diagnostic Issues**

The applicant did not submit an application for an *in vitro* diagnostic device (IVD), as the use of an IVD is not essential to the safe and effective use of tivozanib.

## 5 Nonclinical Pharmacology/Toxicology

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### 5.1. Executive Summary

The nonclinical studies for tivozanib hydrochloride were reviewed on May 24, 2013 under NDA # 204408 (Applicant-owned) for the treatment of patients with advanced renal cell carcinoma (RCC). See Appendix 19.3. In the current executive summary, risk estimates are calculated based on the maximum recommended human dose of 1.34 mg/day for adult patients with *relapsed or refractory* advanced RCC.

Tivozanib hydrochloride is an anticancer agent of the Vascular Endothelial Growth Factor Receptor (VEGFR) Tyrosine Kinase inhibitor class and is being developed for the treatment of advanced renal cell carcinoma. *In vitro* cellular kinase assays demonstrated that tivozanib is an inhibitor of VEGF receptors -1, -2, and -3 (IC<sub>50</sub> 0.107, 0.081, and 0.122 ng/mL, respectively) and other kinases such as c-Kit and PDGFR $\beta$  at higher IC<sub>50</sub>'s (0.83 and 0.88 ng/ml, respectively). The IC<sub>50</sub> of these kinases is well below the C<sub>min</sub> value achieved in RCC patients (16 to 30.9 ng/mL) following repeat dosing at the recommended dose at 1.34 mg/day, suggesting continuous inhibition of these kinases throughout the treatment period.

*In vivo* pharmacodynamic studies in mice and rats bearing human or murine xenograft tumors demonstrated that tivozanib inhibited tumor growth at a dose of 0.2 mg/kg in rats, via inhibition of angiogenesis and vascular permeability. This dose is associated with plasma levels of tivozanib in rodents (C<sub>max</sub> of 70 - 108 ng/ml; AUC of 1640 ng\*hr/ml), which were within range of the C<sub>max</sub> and AUC achieved in patients with solid tumors following repeat dosing at the recommended dose of 1.34 mg/day (C<sub>max</sub> was - 86.9 ng/mL; AUC<sub>0-24</sub> was 1510 ng\*hr/mL).

The selection of animal models to be used in toxicology and safety pharmacology studies (rats and monkeys) was based on PK and/or metabolic profiles of tivozanib. The oral route was utilized in nonclinical studies as this is the intended clinical route of exposure. The tivozanib toxicokinetic profile following repeat oral administration was approximately linear in rats and monkeys, with C<sub>max</sub> and AUC increasing in an approximately dose proportional manner. No gender differences were shown in the rat or monkey. Interspecies differences in the rate of absorption (T<sub>max</sub>) and elimination half-life (t<sub>1/2</sub>) were reported. The elimination t<sub>1/2</sub> in rats (9-45 hours) was greater than that reported in monkeys (8-12 hours), but was considerably shorter than that reported for humans (4.5-5.1 days). To account for these differences, the dosing regimen in the nonclinical toxicology studies was daily as compared to the clinical regimen (once daily, 3 weeks on and 1 week off). *In vitro* distribution studies conducted using animal or human plasma, it was shown that tivozanib bound to plasma proteins at > 97.6%, and protein binding was predominantly to albumin, with low binding to  $\alpha$ -1-acid glycoprotein. Tivozanib mainly partitioned into the plasma/serum component of blood. *In vivo* metabolism studies demonstrated that the parent compound (tivozanib) was the major component in serum and feces of rats and monkeys. Tivozanib appeared to be metabolized mainly by

oxidation, demethylation and glucuronidation. All prominent human metabolites (M1 through M24) were present in both rat and monkey, with the exception of M11, which was unique to human hepatocytes (minor >0.5%), and M10, which was not observed in rat hepatocytes. M14 was present at >10% and was designated as a major metabolite in human, monkey and rat. Comparison of the metabolic profile of tivozanib in liver microsomes showed that monkey most closely resembled the human, followed by the rat. These data provided support for species selection. Excretion studies in rats and monkeys showed that tivozanib was mainly excreted in feces in both species, and through the bile in rats.

In safety pharmacology studies, no effects on respiration rate, tidal volume, neurobehavioral endpoints or physiological parameters were reported in rat studies. In single and repeat-dose cardiovascular studies in telemetered cynomolgus monkeys, a dose of 3 mg/kg (HED= 58 mg/day; 43-fold of the recommended human dose) resulted in increases in systolic, diastolic and mean arterial blood pressure. At doses  $\geq 1$  mg/kg/day in the monkey (HED=19.5 mg/day; 15-fold of the recommended human dose), decreases in heart rate, cardiac output, renal arterial blood flow and cardiac arterial blood flow were reported. A decrease in vascular relaxation response and decrease in sensitivity to acetylcholine were also reported at doses  $\geq 1$  mg/kg/day, which may have played a role in the reported hypertension response in monkeys.

Using the core battery of genetic toxicology studies recommended in ICH guidances, tivozanib was not shown to be mutagenic, aneugenic or clastogenic; however, tivozanib produced changes in chromosomal number (polyploidy, hyperdiploidy) at  $\geq 2$   $\mu\text{g/mL}$  (23-fold times the plasma level at recommended human dose).

In a male and female fertility study in rats, doses  $\geq 0.1$  mg/kg/day resulted in a decrease in animal mating (HED=0.97 mg/day; 0.72-fold of the recommended human dose) and doses  $\geq 0.3$  mg/kg/day produced infertility (HED=2.9 mg/day; 2-fold of the recommended human dose). In an embryo-fetal developmental study in rats, tivozanib was administered during the period of organogenesis. Tivozanib at doses  $\geq 0.03$  mg/kg/day (HED=0.29 mg/day; 0.2fold of the recommended human dose) resulted in maternal toxicity, increases in early and late resorptions, an increase in fetal external malformations (body edema, short tail and kinked tail) and an increase in skeletal developmental delays. In an embryo-fetal developmental study in rabbits, tivozanib at 1 mg/kg/day (HED=19.5 mg/day; 14.6-fold of the recommended human dose) administered orally during the period of organogenesis resulted in fetal malformations including ventricular septal defects, constricted pulmonary artery vessels and distended aorta. No maternal toxicity was reported.

Based on findings in animal studies (embryo-fetal development studies ) and its mechanism of action, FOTIVDA can cause fetal harm when administered to a pregnant woman. It is recommended to advise females of reproductive potential to use effective contraception during treatment with FOTIVDA and for 1 month after the last dose. The duration of contraception use is consistent with the the FDA oncology reproductive toxicology guidance for non-genotoxic

and teratogenic pharmaceuticals, where it recommends a contraception period of 5 half-lives after completion of therapy (111 hours ( $t_{1/2}$ ) X 5 = 23.1 days, rounded to one month).

In repeat-dose general toxicology studies, the toxicity profiles of tivozanib in the rat and monkey showed some overlap. The predominant toxicities in both species were associated with the following systems/organs: adrenal gland, gastrointestinal system (stomach, duodenum, and pancreas), kidney, bone (femur and tibia), liver, brain, pituitary gland, heart, incisors and reproductive system (ovaries and uterus). Clinical pathology changes and body weight decreases were also reported in both species.

Oral administration of tivozanib to rats for 13 weeks resulted in mortalities and severe clinical observations (clinical signs typically associated with morbidity, malocclusion, missing teeth and white teeth) at doses  $\geq 0.1$  mg/kg/day (HED=0.97 mg/day; 0.72-fold of the recommended human dose). The observed dental toxicity correlated with microscopic findings in the incisors of the rats which may have contributed to the reported decreases in body weights and food consumption. The effect on incisors is unlikely to be relevant to targeted patient population (adults) due to the difference in incisor growth patterns in rats and humans. Clinical pathology changes were reported at doses  $\geq 0.03$  mg/kg/day (HED=0.29; 0.21-fold the recommended human dose) and included changes in hematology (increases in RBC and WBC parameters), clinical chemistry (increases in iron metabolism, liver parameters, LDH/creatinine, triglycerides and renal parameters and decrease in protein parameters) and urine parameters (increases in protein, urobilinogen, bilirubin and hyaline casts). At doses  $\geq 0.1$  mg/kg/day (HED=0.97; 0.72-fold the recommended human dose) the target organs with significant toxicity were the adrenal glands, kidney, bone-femur, liver/bile duct, brain, pituitary, incisors, pancreas and duodenum. Less pronounced (lower incidence and/or severity) microscopic findings were reported in the heart, reproductive organs, bone marrow, adrenal medulla and stomach. Partial recovery of most effects was reported at doses  $\geq 0.1$  mg/kg/day, although renal effects were not recoverable at these doses. Toxicities at doses  $\geq 0.3$  mg/kg/day overlapped with those at the lower doses, but were more severe, occurred at a higher incidence and were for the most part not recoverable.

Oral administration of tivozanib in rats for 26 weeks produced non-adverse decreases in body weights, abnormal whitening of the teeth and changes in hematology/clinical chemistry at 0.08 mg/kg/day. No test article-related findings were reported by the end of the treatment or the recovery periods. The doses assessed in this study were low, and given the lack of appreciable toxicity, were considered insufficient to enable an adequate determination of dose-response relationships.

Oral administration of tivozanib in monkeys for 13 weeks produced microscopic findings in the brain and adrenal cortex at doses  $\geq 0.1$  mg/kg/day (HED=1.9 mg/day; 1.4-fold of the recommended human dose). At doses  $\geq 0.3$  mg/kg/day (HED=5.8 mg/day; 4.3-fold of the recommended human dose), adverse clinical signs, decrease in body weight and changes in hematology (increases in RBC, decreases and in WBC parameters), clinical and urine chemistry

parameters (increases in CK, SELA- $\alpha$  &  $\beta$ , iron, phospholipids; decreases in ALP, SDH, total bile acid, amylase, UIBC, U LDH and U creatinine) were reported. The predominant test article-related microscopic findings evident at doses  $\geq$  0.3 mg/kg/day included bone (femur and tibia), gastric system (stomach, duodenum and pancreas), reproductive system (ovary and corpora lutea) and lymphoid organs (lymphoid depletion of thymus, lymph nodes and spleen). The majority of the findings were recoverable after a 2- or 5-week recovery period.

In a 39-week oral toxicity study in monkeys, the highest dose tested 0.1 mg/kg/day (HED=1.95 g/day; 1.5-fold of the recommended human dose) was well tolerated. As with the 26-week rat study, the doses assessed in the 39-week monkey study were low, and given the lack of appreciable toxicity, were considered insufficient to enable an adequate determination of dose-response relationships.

Ocular and cutaneous phototoxicity studies with tivozanib in rats did not show skin or ocular phototoxicity.

The nonclinical data submitted in this NDA are adequate to support approval of FOTIVDA for the proposed indication.

## 5.2. Referenced NDAs, BLAs, DMFs

NDA 204408

X

Eias Zahalka  
Primary Reviewer

X

Tiffany Ricks  
Team Leader

## 6 Clinical Pharmacology

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### 6.1. Executive Summary

Tivozanib hydrochloride is a tyrosine kinase inhibitor of vascular endothelial growth factor (VEGFR)-1, -2, and -3. In the current original NDA submission, the applicant seeks approval of tivozanib for the treatment of patients with relapsed or refractory RCC. The Applicant proposed dosing regimen is 1.34 mg oral once daily (QD) for 3 weeks on and 1 week off, with or without food.

The primary evidence of efficacy and safety is provided by a pivotal randomized, open-label, controlled trial (TIVO-3) in patients with relapsed or refractory advanced RCC, who received prior systemic treatments (2 TKIs, a TKI plus a checkpoint inhibitor or a TKI plus other agent). Safety data included 1008 patients with RCC treated with tivozanib who were enrolled in 6 monotherapy studies that included patients from study TIVO-3 comparing tivozanib to sorafenib.

The clinical pharmacology review focused on dose selection and the acceptability of tivozanib dosing recommendations for general population, for patients with organ dysfunction, and for drug-drug interactions.

#### Recommendations

The office of clinical pharmacology has reviewed the information contained in NDA 212904. This NDA is approvable from a clinical pharmacology perspective. The key review issues with specific recommendations/comments are summarized below:

| Review Issue                                                         | Recommendations and Comments                                                                                                                                                                                                                                                                                                                                                                                           |
|----------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Pivotal and Supportive evidence of effectiveness</b>              | The primary evidence of effectiveness comes from a pivotal phase 3, randomized, open-label, controlled trial (TIVO-3)                                                                                                                                                                                                                                                                                                  |
| <b>General dosing instructions</b>                                   | The proposed dosing regimen of 1.34 mg oral once daily (QD) for 3 weeks on and 1 week off, with or without food is acceptable and is supported by the improvement in PFS, compared to the active control, observed in patients with relapsed or refractory RCC.                                                                                                                                                        |
| <b>Dosing in patient subgroups (intrinsic and extrinsic factors)</b> | <ul style="list-style-type: none"><li>• Patients with hepatic impairment:<ul style="list-style-type: none"><li>○ Mild: No dose adjustment</li><li>○ Moderate: Reduce dose to 0.89 mg oral once daily for 3 weeks on and 1 week off, with or without food</li><li>○ Severe: Avoid use</li></ul></li><li>• Patients with renal impairment:<ul style="list-style-type: none"><li>○ No dose adjustment</li></ul></li></ul> |

|                               |                                                                                                                                                                                 |
|-------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Drug-Drug interactions</b> | CYP3A Inducers: Tivozanib is primarily metabolized by CYP3A4. <ul style="list-style-type: none"><li>• Avoid coadministration of tivozanib with strong CYP3A4 inducer.</li></ul> |
| <b>Labeling</b>               | Generally acceptable, upon the Applicant's agreement to the FDA revisions to the label.                                                                                         |

## 6.2. Summary of Clinical Pharmacology Assessment

### 6.2.1. Pharmacology and Clinical Pharmacokinetics

Tivozanib demonstrated linear pharmacokinetics (PK) in the dose range of 0.89 -1.78 mg following both single dose and repeated doses. At the recommended dosage of 1.34 mg QD, the steady state C<sub>max</sub> (%CV) of Tivozanib was 86.9 (66%) ng/mL and the steady state area under the concentration-time curve (AUC<sub>0-24h</sub>) (%CV) was 1510 (67%) ng\*hr/mL. The plasma elimination half-life (T<sub>1/2</sub>) is 111 hours. Following repeated 1.34 mg QD administration, steady-state was achieved by 14 days after the first dose and accumulation at steady-state is approximately 6- to 7- fold the exposure observed at single-dose levels.

#### ADME properties

**Absorption:** The median time to peak concentration (T<sub>max</sub>) ranged from 3 to 24 hours in most studies. This is most likely due to enterohepatic recirculation of tivozanib, which was also seen in non-clinical mouse, rat and monkey studies. The C<sub>max</sub> of tivozanib decreased by 23% (C<sub>max</sub> GMR 0.77, 95%CI: 0.729-0.824) and the AUC<sub>0-∞</sub> did not change (AUC<sub>0-∞</sub> GMR 1.074, 95%CI: 1.028-1.123) when tivozanib was taken with a high-calorie, high-fat meal (approximately 500-600 fat calories, 250 carbohydrate calories and 150 protein calories) compared to those in the fasted state.

**Distribution:** The typical apparent volume of distribution of tivozanib is 121 L, volume of distribution was found to increase nearly proportionally with body weight. In vitro protein binding of tivozanib is >99%. The blood-to-plasma ratio is 0.495 to 0.615.

**Metabolism:** Tivozanib can be metabolized by CYP3A4 and CYP1A1 in vitro. As CYP1A1 is mainly expressed in extrahepatic tissues such as the lung and intestine, it is unlikely that this isoform would be extensively involved in generating the metabolites observed following incubations with human liver microsomes. Following a single oral dose of 1.34 mg of (160 μCi) of [<sup>14</sup>C]-tivozanib, unchanged tivozanib was the predominant circulating component in serum, ranging from approximately 77.6% to 95.1% (median = 90.1%) of the total radioactivity. Of the minor unknown metabolites detected, each represented less than or equal to a mean of ~4% of the total radioactivity.

**Elimination:** The  $T_{1/2}$  of tivozanib was 111 hours. Typical CL/F was 0.75 L/h.

**Excretion:** Following a single oral dose of 1.34 mg of (160  $\mu$ Ci) of [ $^{14}$ C]-tivozanib to healthy male patients, 79.3% of the radioactive dose was recovered in feces as both unchanged tivozanib (7.82% to 46.1%, median = 26.2%) and metabolites (the predominant metabolites together represented a total of 6.35% to 34.3%, median=20.5%) and 11.8% in urine (unchanged tivozanib not detected).

## 6.2.2. General Dosing and Therapeutic Individualization

### General Dosing

The proposed dosing regimen is 1.34 mg oral once daily (QD) for 3 weeks on and 1 week off, with or without food.

#### Dose Selection Rationale and Dose- and Exposure-Response Relationships

The doses of 0.89, 1.34, and 1.78 mg were evaluated in the first-in-human dose escalation study (Study AV-951-03-B01). The selection of the proposed dose was supported by dose-dependent effect of tivozanib on dose-limiting toxicity and hypertension in the first-in-human study, and also supported by pharmacodynamic analysis, which demonstrated dose-dependent increases in serum VEGF-A levels, dose-dependent decreases in serum soluble VEGFR-2 levels and a dose-dependent reduction in tumor perfusion. Due to the incidence of dose-limiting toxicities (DLTs) at the highest dose level tested (1.78 mg), the 1.34 mg dose of tivozanib was identified as the highest dose level with an acceptable safety/tolerability profile.

With regard to the on/off period, the first-in-human study was initiated with a 4 weeks on/2 weeks off schedule, and then altered to a 3 weeks on/1 week off schedule due to the following reasons: 1) Adverse events in FIH Study AV-951-03-B01 were rapidly reversible upon stopping treatment, supporting a shorter rest period; 2) Nonclinical studies showed that tumors regrew after cessation of tivozanib.

The proposed dosing regimen (1.34 mg oral once daily (QD) for 3 weeks on and 1 week off, with or without food) was subsequently studied in four studies: AV-951-07-201, AV-951-10-202, AV-951-09-301 (TIVO-1), AV-951-15-303 (TIVO-3). The primary evidence of efficacy and safety is provided by pivotal, randomized, open-label, controlled trial (TIVO-3) in patients with relapsed or refractory advanced RCC, who received prior systemic treatments (2 TKIs, a TKI plus a checkpoint inhibitor or a TKI plus other agent). Safety data included 1008 RCC patients treated with FOTIVDA who were enrolled in 6 monotherapy studies that included patients from the pivotal randomized study TIVO-3 comparing tivozanib to sorafenib. The proposed dosage is effective and has a manageable safety profile.

Dose-response relationship was not established, the exposure-response analysis was based on only one dose level, which is the proposed dosage 1.34 mg. Exposure-response analysis demonstrated that increased tivozanib exposure by  $C_{avg}$  quartile was associated with a trend

towards increased PFS, the highest tivozanib exposure quartile (Q4) an estimated relative risk reduction of approximately 33% compared to the lowest tivozanib exposure quartile (Q1). In addition, exposure-dependent increases in rates of hand-foot syndrome (HFS, a.k.a., palmar-plantar erythrodysesthesia [PPE]) was also demonstrated.

The above data supports the selection of the highest dose level with an acceptable safety/tolerability profile, which is the proposed dosing regimen 1.34 mg oral once daily (QD) for 3 weeks on and 1 week off, with or without food.

### Therapeutic Individualization

No clinically significant differences in the PK of tivozanib were observed based on gender, race (93% Caucasian, 3% African American, 2% Asian, 2% others), age (18-84 yrs), body weight (39-158 kg), mild to severe renal impairment, or mild hepatic impairment.

Patients with moderate hepatic impairment eliminated Tivozanib more slowly, mean tivozanib exposure (AUC<sub>t</sub>) increased 1.62-fold. Reduce the recommended dosage of tivozanib to 0.89 mg capsule taken orally once daily for 3 weeks on treatment followed by 1 week off treatment for a 28-day cycle for patients with moderate hepatic impairment.

The effect of severe hepatic impairment on the pharmacokinetics of tivozanib is unknown. For patients with severe hepatic impairment, tivozanib is not recommended.

### Outstanding Issues

None.

## 6.3. Comprehensive Clinical Pharmacology Review

### 6.3.1. General Pharmacology and Pharmacokinetic Characteristics

**Table 3. General Pharmacology and Pharmacokinetics**

| Pharmacology        |                                                                                                                                                                                                                                                                                           |
|---------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Mechanism of Action | Tivozanib is a kinase inhibitor that targets 3 vascular endothelial growth factor receptors (VEGFR1, 2 and 3)                                                                                                                                                                             |
| Active Moieties     | Unchanged tivozanib is the predominant circulating component in serum, ranging from approximately 77.6% to 95.1% (median = 90.1%) of the total radioactivity. Of the minor unknown metabolites detected, each represented less than or equal to a mean of ~4% of the total radioactivity. |
| QT prolongation     | No large (>20 msec) QTc prolongation effect of tivozanib was detected in this QT assessment.<br>The effect of tivozanib was evaluated in an open-label, multiple dose, single arm study in patients with advanced solid tumors (Study                                                     |

|                                                                        | <p># AV-951-10-112). The highest dose evaluated was 1.34 mg (1.34 mg tivozanib free base is equivalent to 1.5 mg tivozanib hydrochloride as cited in table below) once daily for 21 days, which covers the therapeutic exposures of tivozanib. 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.</p> <p>The results from this analysis are supported by the available nonclinical data, categorical analysis, and by-timepoint analysis. Refer to QT-IRT review for more information.</p> <p style="text-align: center;"><b>Table 1: The Point Estimates and the 90% CIs</b></p> <table border="1" style="margin-left: auto; margin-right: auto;"> <thead> <tr> <th>ECG Parameter</th> <th>Treatment</th> <th>Concentration (ng/mL)</th> <th>ΔQTcF (msec)</th> <th>90% CI (msec)</th> </tr> </thead> <tbody> <tr> <td>QTc</td> <td>Tivozanib 1.5 mg*</td> <td>104.1</td> <td>6.9</td> <td>(3.1 to 10.8)</td> </tr> </tbody> </table> | 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) |
|------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------|--------------|-----------------------|--------------|---------------|-----|-------------------|-------|-----|---------------|
| 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)         |              |               |     |                   |       |     |               |
| <b>General Information</b>                                             |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |                       |              |                       |              |               |     |                   |       |     |               |
| Bioanalysis                                                            | Tivozanib in serum was measured using validated LC-MS/MS methods. A summary of the method validation is included as an appendix (19.4.1)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |                       |              |                       |              |               |     |                   |       |     |               |
| Healthy Volunteers vs. Patients                                        | PopPK analysis demonstrated no effect of disease status (healthy, solid tumor, RCC) on the PK of tivozanib.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |                       |              |                       |              |               |     |                   |       |     |               |
| Drug exposure at steady state following the therapeutic dosing regimen | When 1.34 mg was administered daily for 3 weeks on/1 week off in patients with RCC, C <sub>max</sub> was 86.9 (66%) ng/mL and AUC <sub>0-24</sub> was 1510 (67%) ng*hr/mL at steady state.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |                       |              |                       |              |               |     |                   |       |     |               |
| Minimal effective dose or exposure                                     | Not available.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |                       |              |                       |              |               |     |                   |       |     |               |
| Maximal tolerated dose or exposure                                     | 1.34 mg once daily as a monotherapy                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |                       |              |                       |              |               |     |                   |       |     |               |
| Dose proportionality                                                   | Exposure (AUC and C <sub>max</sub> ) of tivozanib generally increased in a dose-proportional manner across the dose range evaluated (0.89 mg to 1.78 mg).                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |                       |              |                       |              |               |     |                   |       |     |               |
| Accumulation                                                           | Accumulation at steady-state is approximately 6- to 7- fold the exposure observed at single-dose levels                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |                       |              |                       |              |               |     |                   |       |     |               |
| Variability                                                            | Population PK modelling showed high variability (82.5%) in mean transit time (MTT) for absorption, likely due to enterohepatic recirculation of tivozanib, but moderate variability in distribution and elimination parameters (40.5% and 28.1% for CL/F and V1/F, respectively).                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |                       |              |                       |              |               |     |                   |       |     |               |
| <b>Absorption</b>                                                      |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |                       |              |                       |              |               |     |                   |       |     |               |
| Oral                                                                   | Absolute oral bioavailability has not been determined.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |                       |              |                       |              |               |     |                   |       |     |               |
| Bioequivalent                                                          | The proposed to-be-marketed formulation is 0.89 mg and 1.34 mg strength capsules.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |                       |              |                       |              |               |     |                   |       |     |               |

|                                                         |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |                       |                      |
|---------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------|----------------------|
|                                                         | (b) (4)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |                       |                      |
|                                                         | the capsule formulation is used throughout the clinical studies and is the intended commercial formulation.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |                       |                      |
| Oral T <sub>max</sub>                                   | The pharmacokinetics (PK) of tivozanib in humans are characterized by a variable absorption period with a median time to peak serum concentration (T <sub>max</sub> ) ranging from approximately 3 to 24 hours in most studies.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |                       |                      |
| Food Effect for 1.34 mg capsule fed/fasted GMR (90% CI) | Negative food effect                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |                       |                      |
|                                                         | C <sub>max</sub>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | AUC <sub>0-last</sub> | AUC <sub>0-∞</sub>   |
|                                                         | 0.775 (0.729, 0.824)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | 1.051 (0.998, 1.106)  | 1.074 (1.028, 1.123) |
| Substrate transporter systems [in vitro]                | Tivozanib is neither a substrate nor inhibitor of the transporter proteins MDR1 (P-gp), OCT1, OATP1B1, OATP1B3 and BSEP. Furthermore, tivozanib is not an in vitro inhibitor of OAT1, OAT3, OCT2, MATE1 and MATE2-K nor substrate of MRP2 and BCRP. Tivozanib inhibits the transporter BCRP in vitro, however, the theoretical GI concentration (1.05 μM) is < 2-fold greater than the in vitro IC <sub>50</sub> (0.68 μM) for BCRP, therefore inhibition of BCRP is likely to be incomplete, also, because of the low solubility and low permeability of tivozanib, the GI concentration is likely lower than the theoretical GI concentration. Therefore, the inhibition of BCRP is considered clinically insignificant. |                       |                      |
| <b>Distribution</b>                                     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |                       |                      |
| Volume of Distribution                                  | Volume of distribution was found to increase nearly proportionally with body weight. Typical value (95% CI) is 123 (121-126) L.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |                       |                      |
| Plasma Protein Binding                                  | >99%                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |                       |                      |
| Blood to Plasma Ratio                                   | 0.495 - 0.615                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |                       |                      |
| <b>Elimination</b>                                      |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |                       |                      |
| Half-life                                               | The half life of tivozanib is 111 hours. Females had a longer estimated T <sub>1/2</sub> (129 hours) compared to males (110 hours).                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |                       |                      |
| Clearance                                               | The apparent clearance (CL/F) is 0.75 L/h. Females had a 24.5% lower clearance (typical value 0.651 L/h) versus males (typical value 0.862 L/h).                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |                       |                      |
| <b>Metabolism</b>                                       |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |                       |                      |
| Primary metabolic pathway(s)                            | Tivozanib is primarily metabolized by CYP3A4. UGT-mediated metabolism of tivozanib required an initial oxidative (Phase 1) step catalyzed by CYP450.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |                       |                      |
| Inhibitor/Inducer                                       | Tivozanib does not inhibit CYP isoforms 1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6 and 3A4 in a clinical meaningful way. Tivozanib was not found to be a strong inhibitor of UGT activities, UGT isoforms not identified.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |                       |                      |

|                            |                                                                                                                                                                                                                                                                                                  |
|----------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                            | Tivozanib does not induce CYP1A, CYP2B6, CYP2C9, CYP2C19 or CYP3A.                                                                                                                                                                                                                               |
| <b>Excretion</b>           |                                                                                                                                                                                                                                                                                                  |
| Primary excretion pathways | Following a single oral dose of 1.34 mg radiolabeled tivozanib to healthy male patients, the majority (mean 79.3%) of [ <sup>14</sup> C]-tivozanib was excreted in the feces as both unchanged tivozanib and metabolites, while the remainder (mean 11.8%) was excreted as metabolites in urine. |

### 6.3.2. Clinical Pharmacology Questions

#### **Does the clinical pharmacology program provide supportive evidence of effectiveness?**

Yes, the primary evidence of effectiveness was obtained from a pivotal, randomized, open-label, controlled trial (TIVO-3). A summary of the clinical effectiveness and safety results based on Study TIVO-3 are provided in Section 7.

Exposure-response analyses for efficacy demonstrated exposure-dependent increases in progression-free survival (PFS), providing supportive evidence of effectiveness for tivozanib. Exposure-response analyses for safety demonstrated exposure-dependent increases in rates of hand-foot syndrome (HFS, a.k.a., palmar-plantar erythrodysesthesia [PPE]). In addition, the proposed dose reduction strategy (1.34 mg to 0.89 mg) to manage tolerable ≤grade 3 AEs was proposed and it appears reasonable.

#### **Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?**

Yes, the proposed dosing regimen is considered appropriate from the following aspects:

- 1) The dose-dependent, dose-limiting toxicities (DLTs) and hypertension in the first-in-human study, as well as the dose-dependent increases in serum VEGF-A levels, dose-dependent decreases in serum soluble VEGFR-2 levels, and dose-dependent reduction in tumor perfusion supported the selection of a highest dose level (1.34 mg) with an acceptable safety/tolerability profile. Due to the incidence of DLTs at the highest dose level tested (1.78 mg) in the dose-escalation study, and the acceptable safety profile in patients with RCC in the pivotal TIVO-3 study, the 1.34 mg dose of tivozanib was considered appropriate.
- 2) With regard to the on/off period, the first-in-human study was initiated with a 4 weeks on/2 weeks off schedule, and then altered to a 3 weeks on/1 week off schedule due to the following reasons: a) Adverse events in FIH Study AV-951-03-B01 were rapidly reversible upon stopping treatment, supporting a shorter rest period; b) Nonclinical

studies showed that tumors regrew after cessation of tivozanib. The proposed treatment schedule was considered appropriate due to the manageable safety profile.

- 3) The proposed dosage of 1.34 mg QD, 3 weeks on, 1 week off is supported by the improvement in PFS, compared to the active control in the pivotal TIVO-3 study. The high relative dose intensity (88.3%) despite the longer mean exposure than the active control, suggests that tivozanib is well-tolerated.

**Is an alternative dosing regimen or management strategy required for subpopulations based on intrinsic patient factors?**

Gender

Although gender has an effect on the clearance of tivozanib, females had a 24.5% lower clearance (typical value 0.651 L/h) versus males (typical value 0.862 L/h). The effect of gender on PFS was not clinically meaningful, therefore, a dose adjustment is not warranted.

Hepatic Impairment

Yes, for patients with moderate hepatic impairment, the dosage should be reduced to 0.89 mg oral once daily (QD) for 3 weeks on and 1 week off, with or without food; for patients with severe hepatic impairment, tivozanib is not recommended.

The effect of hepatic impairment on the PK of tivozanib was assessed in a dedicated hepatic impairment study and by population PK analysis.

In the dedicated study, the patients were originally classified according to Child-Pugh Scores, there were 8 patients with mild hepatic impairment (Child-Pugh A), 8 patients with moderate hepatic impairment (Child-Pugh B) and 6 patients with severe hepatic impairment (Child-Pugh C). Results showed that the exposure to tivozanib in patients with mild hepatic impairment was similar to that in patients with normal hepatic function (GMR of  $AUC_{0-\infty}$ : 1.1 ). However, tivozanib was eliminated more slowly in patients with moderate or severe hepatic impairment, mean tivozanib exposure ( $AUC_{0-\infty}$ ) increased 2.2-fold in patients with moderate (Child-Pugh B) hepatic impairment and 3.4-fold in patients with severe (Child-Pugh C) hepatic impairment.

After re-classifying the patients in the dedicated study by NCI-ODWG criteria, there were 12 patients with mild hepatic impairment, 5 patients with moderate hepatic impairment, 0 patients with severe hepatic impairment. Mean tivozanib exposure ( $AUC_{0-\infty}$ ) increased 1.79-fold in patients with mild hepatic impairment and 3.49-fold in patients with moderate hepatic impairment. The effect of hepatic impairment on the clearance of tivozanib was larger when patients were classified by NCI-ODWG criteria compared to Child-Pugh criteria in the dedicated study.

Therefore, in the PopPK analysis, NCI-ODWG criteria was used to classify the patients, not only because that dosing recommendation based on NCI-ODWG criteria is more conservative, given

the larger fold changes in AUC observed, but also that the majority of the patients were cancer patients. In the whole PopPK dataset, there were 570 patients with normal hepatic function, 83 patients with mild hepatic impairment, 10 patients with moderate hepatic impairment, 0 patients with severe hepatic impairment. The PopPK analysis indicated that mild hepatic impairment did not have an effect on the tivozanib CL/F, while patients with moderate hepatic impairment were found to have a 38.9% lower tivozanib CL/F compared to patients with normal hepatic function or mild hepatic impairment.

The PopPK analysis, using all data with more patients for both mild hepatic impairment and moderate hepatic impairment, provided a reliable estimate for the hepatic impairment effect, given disease status was not found to be a significant covariate. Therefore, simulations were conducted based on the PK metrics generated from PopPK analysis. Simulation results indicated that 0.89 mg once daily (QD) for 3 weeks on and 1 week off in patients with moderate hepatic impairment is estimated to result in tivozanib exposure comparable to that in patients with normal hepatic function treated with 1.34 mg QD tivozanib for 3 weeks on and 1 week off. Therefore, based on the safety profile in the clinical trials, 0.89 mg once daily (QD) for 3 weeks on and 1 week off is recommended for patients with moderate hepatic impairment.

**Are there clinically relevant food-drug or drug-drug interactions, and what is the appropriate management strategy?**

There is no clinically relevant food-drug interactions.

Tivozanib is primarily metabolized by CYP3A4. Coadministration of tivozanib with ketoconazole did not have an effect on tivozanib exposure. Coadministration of tivozanib with rifampin resulted in decreased tivozanib exposure ( $AUC_{0-\infty}$ ) by approximately 50%. Avoid coadministration of tivozanib with strong CYP3A4 inducers.

Effect of Food on Tivozanib

The  $C_{max}$  of tivozanib decreased by 23% ( $C_{max}$  GMR 0.77, 95%CI: 0.729-0.824) and the  $AUC_{0-\infty}$  did not change ( $AUC_{0-\infty}$  GMR 1.074, 95%CI: 1.028-1.123) when tivozanib was taken with a high-calorie, high-fat meal (approximately 500-600 fat calories, 250 carbohydrate calories and 150 protein calories) compared to those in the fasted state. Tivozanib is recommended to be administered with or without food.

Effect of CYP3A Inhibitors on Tivozanib

Coadministration of tivozanib 1.34 mg single dose with ketoconazole 400 mg once daily (a strong CYP3A inhibitor) did not have an effect on tivozanib exposure.  $C_{max}$  GMR 0.966, 95%CI: 0.905-1.031,  $AUC_{0-\infty}$  GMR 1.049, 95%CI: 1.005-1.095.

Effect of CYP3A inducers on Tivozanib

Coadministration of tivozanib 1.34 mg single dose with rifampin 600 mg once daily (a strong CYP3A inducer) decreased tivozanib exposure ( $AUC_{0-\infty}$ ) by approximately 50%.  $C_{max}$  GMR 1.084, 95%CI: 0.998-1.178,  $AUC_{0-\infty}$  GMR 0.480, 95%CI: 0.448-0.516.

**Question on clinically relevant specifications (TBD)?**

None.

**X**

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Miao Zhao  
Primary Reviewer

**X**

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Jeanne Fourie Zirkelbach  
Team Leader

## 7 Sources of Clinical Data and Review Strategy

### 7.1. Table of Clinical Studies

**Table 4. Listing of Clinical Trials Relevant to this NDA**

| Study number                                             | NCT no      | Description of trial <sup>1</sup>                                                                                                | Regimen                                                             | Study endpoints                | Treatment Duration                     | Patients enrolled (N) |
|----------------------------------------------------------|-------------|----------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------|--------------------------------|----------------------------------------|-----------------------|
| <i>Controlled Studies to Support Efficacy and Safety</i> |             |                                                                                                                                  |                                                                     |                                |                                        |                       |
| AV-951-15-303 (TIVO-3)                                   | NCT02627963 | Phase 3 randomized trial, tivozanib vs. sorafenib, in relapsed/refractory patients                                               | tivozanib hydrochloride 1.5 mg orally 3-weeks-on-1-off <sup>2</sup> | PFS assessed by BIRC           | Until disease progression <sup>3</sup> | 350                   |
| <i>Studies to Support Safety</i>                         |             |                                                                                                                                  |                                                                     |                                |                                        |                       |
| AV-951-09-301 (TIVO-1)                                   | NCT01030783 | Phase 3 randomized trial, tivozanib vs. sorafenib, in treatment-naïve patients                                                   | tivozanib hydrochloride 1.5 mg orally 3-weeks-on-1-off <sup>2</sup> | PFS assessed by BIRC           | Until disease progression <sup>3</sup> | 517                   |
| AV-951-09-902                                            | NCT01076010 | Phase 3 extension study of TIVO-1                                                                                                |                                                                     | Drug exposure and safety       | Until disease progression <sup>3</sup> | 161                   |
| AV-951-10-202                                            | NCT01297244 | Phase 2 and biomarker study in treatment-naïve patients                                                                          |                                                                     | Biomarkers and CBR at 6 months | 6 months                               | 105                   |
| AV-951-12-205 (TAURUS)                                   | NCT01673386 | Phase 2 randomized, double-blind, 2-arm crossover patient preference study (tivozanib vs. sunitinib) in treatment-naïve patients |                                                                     | Patient preference             | 12 weeks (each drug)                   | 58                    |
| AV-951-07-201                                            | NCT00502307 | Phase 2 placebo-controlled discontinuation trial in treatment-naïve patients                                                     |                                                                     | AEs, ORR, CBR at 16 weeks      | 16 weeks                               | 272                   |

<sup>1</sup>All patients were treated for advanced RCC

<sup>2</sup>Three weeks on, 1 week off of every 4-week cycle

<sup>3</sup>Until disease progression, death, or unacceptable toxicity

Abbreviations: AEs, adverse events; BIRC, blinded independent radiology review committee; CBR, clinical benefit rate (percent of patients remaining progression-free); ORR, objective response rate; PFS, progression-free survival

## 7.2. Review Strategy

Dr. Elaine Chang conducted the clinical review and Dr. Lijun Zhang conducted the statistical review.

The clinical and statistical review included the following:

1. Literature review of advanced relapsed and refractory RCC.
2. Research of the FDA database for the regulatory history of the tivozanib IND 075547 and review of the ODAC materials and transcript for the TIVO-1 review, and meeting minutes conducted during drug development.
3. Review of applicant submitted CSR, protocol, protocol amendments, statistical analysis plan, and selected datasets for TIVO-3 and TIVO-1.
4. Review of selected case report forms (CRFs) for TIVO-3.
5. Review of selected patient narratives for serious adverse events and deaths in TIVO-3.
6. Review of the Clinical Outcomes Assessment (COA) data submitted for TIVO-1.
7. Review of response to clinical, biostatistical, and select clinical pharmacology queries sent to applicant.
8. Review of consultation reports including from the Office of Scientific Investigations, Interdisciplinary Review Team for Cardiac Safety Studies (QT Study Review), and DRISK.

## 8 Statistical and Clinical and Evaluation

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### 8.1. Review of Relevant Individual Trials Used to Support Efficacy

#### 8.1.1. TIVO-3 (AV-951-15-303)

##### Trial Design

Study TIVO-3 was an open-label, randomized, controlled, multi-national, parallel-arm study to compare treatment with tivozanib to treatment with sorafenib in adult patients with histologically or cytologically confirmed RCC with a clear cell component who failed 2 or 3 prior systemic regimens, including a TKI other than sorafenib or tivozanib.

Patients were randomized 1:1 to receive either tivozanib or sorafenib using the Interactive Web Response System (IWRS). Randomization was stratified by the following factors:

- IMDC prognostic category (favorable vs. intermediate vs. poor)
- Prior therapy (2 prior TKIs vs. a prior checkpoint inhibitor plus a TKI vs. a prior TKI plus any other systemic agent)

Treatment began within 14 days of randomization. Tivozanib was administered 1.5 mg orally daily 3 weeks on/ 1 week off in each 4-week cycle and sorafenib 400 mg BID was administered orally continuously throughout each cycle. Note that 1.5 mg in the protocol refers to the dose of tivozanib hydrochloride, which is equivalent to the recommended dosage of 1.34 mg, referring to tivozanib free base.

Eligible patients were required to have recurrent metastatic RCC with a clear cell component that had progressed after 2 or 3 prior systemic regimens, one of which included a VEGFR TKI other than sorafenib or tivozanib. Postoperative or adjuvant systemic therapy was not counted as a prior therapy unless a recurrence was detected within 6 months of completion of adjuvant treatment. Patients were also required to have measurable disease per RECIST criteria and ECOG performance status of 0 or 1.

Key exclusion criteria included untreated brain metastases, significant cardiovascular disease (symptomatic left ventricular failure, severe angina or acute coronary syndrome within 6 months prior to trial enrollment, uncontrolled hypertension defined as systolic blood pressure [sBP] >150 mmHg or diastolic blood pressure [dBp] >100 mmHg on 2 or more anti-hypertensive medications, documented on 2 consecutive measurements taken at least 2 hours apart, or cardiac arrhythmias requiring anti-arrhythmic medications, except for well-controlled atrial fibrillation), grade  $\geq$  2 bleeding within 6 months prior, non-healing wound, inflammatory bowel disease or risk/history of gastrointestinal perforation or fistula, thromboembolic event or bleeding disorder within 6 months prior, and patients with HIV infection or taking immune suppressive therapy for organ transplant.

Patients were treated until a discontinuation criterion was met. Discontinuation criteria included documented disease progression or significant clinical deterioration indicative of progressive disease, unacceptable toxicity considered by the investigator to require removal of the patient from the trial, and treatment interruption for > 4 weeks. Patients with stable disease or with objective response at the time of treatment discontinuation, who discontinued for reasons other than radiological evidence of progressive disease, continued to have periodic tumor assessments.

Radiology assessments (CT scan or MRI) were performed every 8 weeks following Cycle 1, Day 1 to assess disease status until documented radiographic disease progression. Scans were evaluated by a blinded independent radiology review committee (BIRC).

### **Study Endpoints**

The primary efficacy endpoint of the study was progression-free survival (PFS) per BIRC assessment based on RECIST v 1.1. PFS was defined as the time from randomization to the first date of radiological disease progression or death date (due to any reason), whichever occurred earlier.

Secondary endpoints included overall survival (OS) and objective response rate (ORR).

OS was defined as the time from randomization to the date of death due to any reason.

ORR was defined as the proportion of patients with a best overall response of confirmed complete response or a confirmed partial response, according to the RECIST v1.1 criteria per BIRC assessment.

### **Statistical Analysis Plan**

#### Sample Size Consideration

The study was designed to have 90% power to detect a hazard ratio (HR) of 0.67 for PFS at a two-sided significance level of 5%. Based on an assumed median PFS of 4 months in the sorafenib arm, this targeted treatment effect represents an increase in the median PFS of approximately 2 months (4 months vs. 6 months) in the tivozanib arm. With that, approximately 255 PFS events were required for the primary analysis. A total of 322 patients were planned to be randomized.

Per the statistical analysis plan (version 5), the final OS analysis was to be conducted using a cutoff date of May 1<sup>st</sup>, 2020. Based on an estimate of approximately 4 OS events occurring per month, approximately 263 OS events would occur at that time. That would have 64% power to detect a hazard ratio of 0.75 at a two-sided significance level of 0.05 for OS.

#### Analysis Populations

The primary analysis population for all efficacy endpoints was the intent-to-treat (ITT) population. All randomized patients were to be included in the ITT population. Patients were to be grouped according to the treatment assigned at randomization.

A sensitivity analysis population to be used for the primary efficacy endpoint was the per protocol (PP) population. This population was defined as all randomized patients who received at least 8 weeks of protocol treatment, had no major protocol deviations that would confound the effects of treatment, and met all eligibility criteria. Patients were to be analyzed as treated.

The primary analysis population for safety was the safety analysis population. This population included all patients who received at least one dose of study drug, with treatment assignment designated according to actual study treatment received.

### Efficacy Analysis Methods

The primary efficacy endpoint, PFS per BIRC, was to be summarized using the Kaplan-Meier method, and compared between the two treatment arms using a log-rank test stratified by the randomization stratification factors, i.e., IMDC risk category and prior therapy, as collected in the IWRS system. The treatment effect size was to be estimated by hazard ratio with a two-sided 95% confidence interval derived from a stratified Cox proportional hazards model with the same two stratification factors used in the stratified log-rank test.

PFS was to be censored following the rules below in the primary analysis:

- If there were no tumor assessments after randomization, PFS would be censored on the date of randomization.
- If a patient was known to be alive and progression-free, PFS would be censored on the day of the last tumor assessment.
- If a patient was given anti-tumor treatment (anti-cancer surgery/procedure, anti-cancer radiotherapy, and anti-cancer systemic therapy other than the study treatment) prior to disease progression or death, PFS would be censored on the date of the last tumor assessment prior to the start date of the anti-tumor treatment.
- If treatment follow-up ceased prior to objective disease progression, PFS would be censored on the date of the last tumor assessment.
- If a patient missed 2 or more consecutive post-baseline tumor assessments and the following assessment was disease progression, PFS would be censored on the date of the last tumor assessment.

Secondary endpoints included OS, ORR, and duration of response (DOR). OS was to be analyzed in the same manner as for PFS; i.e., the two treatment arms were compared using the stratified log-rank test and the hazard ratio was estimated using the stratified Cox proportional hazards model. The number and proportion of patients achieving confirmed response (i.e., confirmed complete response or partial response) were to be summarized and compared between treatment arms using a Cochran-Mantel-Haenszel (CMH) test with the same stratification factors used for the PFS analysis. Duration of response was to be summarized for patients who have achieved a confirmed response.

### Interim Analysis

An interim analysis was to be conducted after 128 PFS events were observed for futility evaluation. A Lan-DeMets spending-type function with an O'Brien-Fleming stopping boundary was applied at this interim look. There was no interim efficacy analysis for PFS.

Two interim analyses were planned for OS in the final version of the study SAP. The first interim analysis was to be conducted at the time of the primary PFS analysis and the 2<sup>nd</sup> interim analysis was to be conducted after all patients were followed for at least 2 year. The final analysis was to be conducted at a pre-specified cutoff date of May 1<sup>st</sup>, 2020. A Lan-DeMets spending-type function with an O'Brien-Fleming stopping boundary was used for OS interim analyses.

### Multiplicity Adjustment

There was no multiplicity adjustment for secondary endpoints. PFS was the only primary endpoint and it was tested at 2-sided alpha of 0.05. The secondary endpoints, including overall survival, were intended to provide supportive evidence. All secondary endpoints were assessed without adjustment for multiple comparison.

### **Reviewer comments:**

*The sample size calculation and analysis plan for the primary endpoint of PFS is acceptable.*

*The analysis plan for OS has been revised several times when the study was ongoing. In the initial SAP, the study only planned one interim OS analysis at the time of PFS analysis. Due to the observed negative trend of OS at the time of the first interim analysis, the applicant revised the statistical analysis plan by considering the original planned final OS analysis as the second interim analysis and adding a new final OS analysis with longer follow-up. See the SAP amendment summary table for details. The change of analysis plan for OS could inflate the overall type I error rate if the study had intended to make any efficacy claims on OS. Per the statistical design, the study did not allocate any alpha for OS tests and was not adequately powered for OS analyses; therefore, no statistical inference could be made for OS. Results of all secondary endpoints are considered exploratory. Overall, the statistical analysis plan appears acceptable.*

### **Protocol Amendments**

A summary of important changes implemented under each amendment are provided in the table below. The first distributed protocol was Version 2 (October 2015). A total of 161 patients were randomized during the time that Version 2 was in use, including 3 patients enrolled under France-specific protocol amendment 2.1 and 13 patients enrolled under UK-specific protocol amendment 2.2. Subsequently, a total of 189 patients were randomized during the time that Version 3 was in use, including 10 patients enrolled under France-specific protocol amendment 3.1 and 16 patients under UK-specific protocol amendment 3.2. No patients were enrolled under Version 4.

### **Table 5. Protocol Amendment Summary**

| Protocol version (stamp date) | Major Changes:                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
|-------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Version 1<br>(26 Aug 2015)    | N/A                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
| Version 2<br>(01 Oct 2015)    | <ul style="list-style-type: none"> <li>• Changes made in response to FDA’s Meeting Comments (14 May 2015)                             <ul style="list-style-type: none"> <li>○ Removed statement that limited palliative radiation therapy would be allowed on protocol (initiation of radiotherapy is considered evidence of disease progression)</li> <li>○ Added collection of PK samples at Cycle 1 Day 1 and 15</li> </ul> </li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| Version 3<br>(03 July 2016)   | <ul style="list-style-type: none"> <li>• Changed the start day of treatment from within 10 days to within 14 days after randomization.</li> <li>• Changed minor aspects of inclusion and exclusion criteria                             <ul style="list-style-type: none"> <li>○ Added “Subjects must be off all systemic anti-cancer therapy or radiotherapy for at least 2 weeks”</li> <li>○ Removed exclusion of mixed tumor containing predominantly sarcomatoid histology</li> <li>○ Added “packed red blood cell transfusion is permitted” as a clarification after hemoglobin threshold requirement</li> </ul> </li> <li>• Added “Further management is at the discretion of the investigator, who may discuss this with the medical monitor if necessary” in the dose modification section</li> <li>• Added “A baseline imaging study of the brain is required” (previously only required if patients had history of brain metastasis or symptoms).</li> </ul> |
| Version 4<br>(01 Oct 2018)    | <ul style="list-style-type: none"> <li>• Changed the primary data analysis to be based on data cutoff on October 4, 2018, with a targeted number of 242 PFS events. According to the previous version, the primary data analysis should be done 255 events. “The reasons given were that the current patients have been on study for at least one year and may not progress for some time, and that the small reduction in events at the time of final analysis was unlikely to materially affect the results... Performing the analysis now will reduce the power of the study by approximately 2% (99 vs 90%).” See SAP Version 3 below.</li> </ul>                                                                                                                                                                                                                                                                                                                  |

**Reviewer comment:** *The amendments were generally reasonable and do not impact the integrity of the trial results.*

The first version of the statistical analysis plan was released on 10 June 2016 and amended five times thereafter. The major changes in each amendment are summarized in Table 6.

**Table 6. SAP Amendment Summary**

| SAP version (stamp date)         | Major Changes:                                                                                                                                                                                                                                                                                     |
|----------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Version 2<br>(27 September 2016) | <ul style="list-style-type: none"> <li>• Updated the best overall response criteria to align with the RECIST v1.1 guidelines</li> <li>• Added an exploratory analysis of PFS on the safety population to account for patients that were randomized but not dosed due to external issues</li> </ul> |

|                                                                           |                                                                                                                                                                                                                                                                                                                                  |
|---------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Version 3<br>(01 October 2018)                                            | <ul style="list-style-type: none"> <li>Reflected the administrative change specified in the protocol version 4.0: a previously unspecified data cut-off date for the primary analysis was established to be 04 October 2018 with a targeted number of 242 PFS events per the study steering committee recommendation.</li> </ul> |
| Version 4<br>(21 February 2019)                                           | <ul style="list-style-type: none"> <li>Changed the originally planned final OS analysis (after all patients have been on study for at least two years) to be the secondary interim analysis of OS. The new final OS analysis was to be performed when a total of 75% of patients died (263 OS events)</li> </ul>                 |
| Version 5<br>(08 November 2019)                                           | <ul style="list-style-type: none"> <li>Revised timing of the final OS analysis to be May 1, 2020 (approximately 263 events)</li> </ul>                                                                                                                                                                                           |
| Version 6<br>(11 December 2019)                                           | <ul style="list-style-type: none"> <li>Revised PFS and OS censoring rules</li> <li>Added an unstratified OS sensitivity analysis</li> </ul>                                                                                                                                                                                      |
| Source: NDA 212904, Module 5.3.5.1: Documentation of Statistical Methods. |                                                                                                                                                                                                                                                                                                                                  |

### Reviewer Comments

*The FDA noted that the OS analysis plan was revised after the first interim analysis results were available. In general, the FDA does not recommend revising analysis plan of major endpoints based on unblinded data if not pre-specified. However, given that in this study analyses of OS were to provide supportive evidence on efficacy and safety, and no efficacy claims were to be made on OS, and an OS analysis based on more mature data is expected to have a more accurate overall estimate of survival for the totality of the trial, the revision appeared acceptable in this application.*

*In the SAP Amendment 6, the Applicant revised censoring rules for the primary PFS analysis by adding a censoring rule for missing 2 or more visits per FDA's recommendation. As this revision occurred after unblinding PFS data in 2018, the applicant conducted a sensitivity PFS analysis, in which this censoring rule was removed, to evaluate its impact and results are shown in Table 14. This approach appeared acceptable.*

### 8.1.2. Study Results

#### Compliance with Good Clinical Practices

The sponsor made a formal statement that study was conducted in compliance with ICH E6 current Good Clinical Practice and the principles of the Declaration of Helsinki or the laws and regulations of the country in which the research was conducted, whichever afforded the greater protection to the individual. Informed consent was obtained from all patients prior to initiation of the study.

#### Financial Disclosure

There was no financial information (equity interest, significant payments of other sorts, other compensation by the sponsor and propriety) to disclose for the 802 clinical investigators who participated in TIVO-3, as reported on FDA Form 3454. See Section 19.2.

OSI's inspections include review of financial disclosures to verify documentation and ensure processes are in place to update financial disclosures/interests as needed.

### Data Quality and Integrity

The overall data quality and integrity are acceptable to the reviewers. The submitted datasets are generally consistent, and variables are clearly labeled and/or explained. Based on the submitted data and reports, the reviewers believe that the analyses and results are reliable for regulatory decision making.

The electronic submission including Protocols, Statistical Analysis Plan (SAP), Clinical Study Reports (CSRs) and SAS transport datasets for the NDA submission are located in the network path: \\CDSESUB1\evsprod\NDA212904\0001.

These sources were utilized to perform the clinical and statistical review of this application.

FDA inquired the sponsor about the impact of the communication failure between (b) (4) software systems used to facilitate imaging measurements and import the measurement data into eCRFs. (b) (4) had several discussions with FDA regarding this issue, (b) (4)

(b) (4) For TIVO-3, the number of measurement discrepancies identified was 6 of 21,811 measurements (discrepancy incident rate percentage: 0.03%). Per (b) (4) and sponsor review, none of the discrepancies required action to be taken for the PFS analysis, and thus the communication failure had no impact on the PFS analysis in TIVO-3.

### Patient Disposition

Between May 2016 and August 2017, 457 patients (456 unique patients) were screened for TIVO-3 and 351 patients (350 unique patients) were randomized. For the 106 patients who were screened but not enrolled, reasons for screen failure were not captured by the electronic data capture system and therefore not included in any dataset. However, because FDA inquired about these details via an Information Request, the sponsor provided a listing of screened patients, date of screening, and reason for screen failure. Reasons that patients were ineligible for enrollment are summarized below.

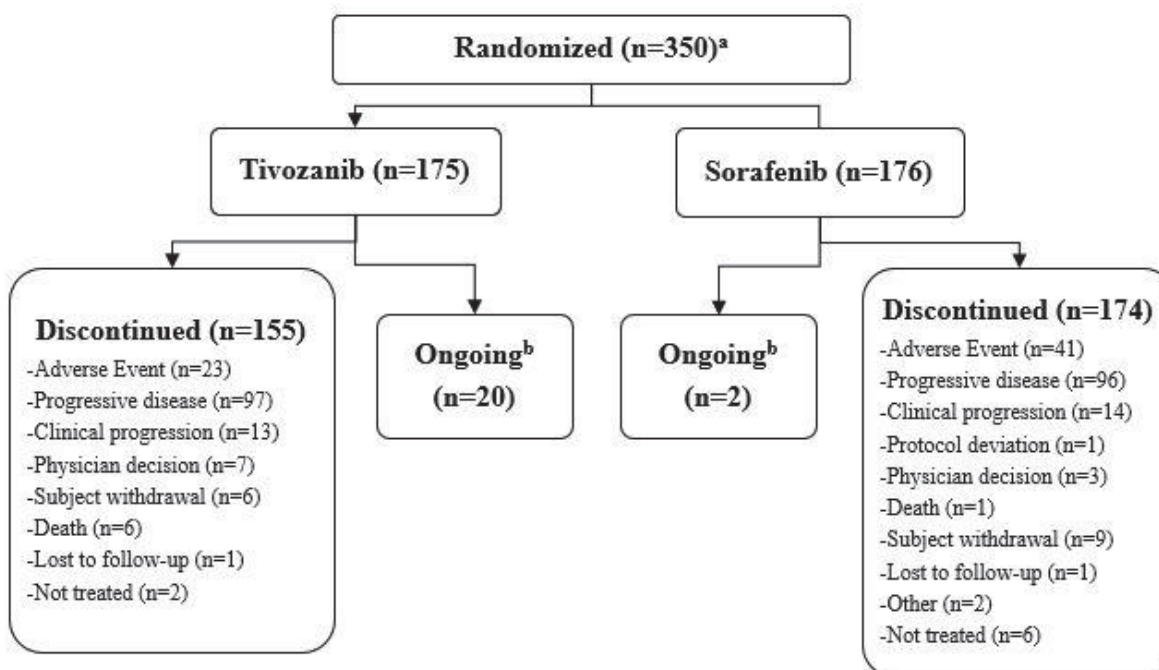
- General conditions: 40/106 (38%)
- Lab abnormalities: 25/106 (24%)
- Systemic disorder: 16/106 (15%)
- Prior therapy: 10/106 (10%)
- ECOG PS > 1: 9/106 (8%)
- No measurable disease per RECIST 1.1: 4/106 (4%)
- Inadequate recovery from prior surgery: 1/106 (1%)

**Reviewer comment:** Significant regional variability was apparent in reasons for screen failure.

For example, “general conditions” comprised reason for screen failure in half of patients, while in other regions, “systemic disorder” comprised reason for screen failure in half of patients, suggesting that these reasons were not well-defined and may be interchangeable depending on the interpretation of the investigator.

Of the 350 patients enrolled, 175 patients were randomized to the tivozanib arm and 175 patients were randomized to the sorafenib arm. Eight (8) patients (2 in the tivozanib arm and 6 in the sorafenib arm) were randomized but not treated. Twenty patients (11%) in the tivozanib arm and 2 patients (1.1%) in the sorafenib arm remained on study drug treatment as of the August 15, 2019 data cutoff date. Patient disposition is shown in the figure.

**Figure 1. Patient Disposition (as of August 15, 2019), TIVO-3**



<sup>a</sup>One patient was randomized twice: first to the tivozanib arm and not dosed, then to the sorafenib arm and dosed. This patient was reported in the intent-to-treat population under tivozanib and in the safety population under sorafenib.

<sup>b</sup>Patients continued until progressive disease or discontinued for other reasons.

As of the May 1, 2020 cutoff, 14 patients (13 in the tivozanib arm and 1 in the sorafenib arm) were receiving ongoing treatment with the study drug.

### Protocol Violations/Deviations

Major protocol deviations were defined as those that affected the study conduct or

interpretation of the study results. The occurrence of major protocol deviations was similar, 26% and 33%, in the tivozanib and sorafenib arms, respectively (Table below).

**Table 7. Protocol Deviations in the ITT Population, TIVO-3**

|                                      | <b>Tivozanib<br/>(n=175)</b> | <b>Sorafenib<br/>(n=175)</b> |
|--------------------------------------|------------------------------|------------------------------|
| Any Major Protocol Deviations, n (%) | 46 (26)                      | 57 (33)                      |
| Inclusion/Exclusion Criteria         | 20 (11)                      | 22 (13)                      |
| Informed Consent                     | 11 (6.3)                     | 10 (5.7)                     |
| Prohibited Medications/Treatments    | 9 (5.1)                      | 15 (8.6)                     |
| Procedures/Tests                     | 1 (0.6)                      | 6 (3.4)                      |
| Visit Schedule                       | 2 (1.1)                      | 3 (1.7)                      |
| Withdrawal Criteria                  | 0                            | 2 (1.1)                      |
| Serious Adverse Event                | 8 (4.6)                      | 7 (4.0)                      |

Source: ADDV.xpt and CSR Table 14.1.2

**Reviewer comment:** Overall, the deviations that did occur were unlikely to impact overall study results.

### Table of Demographic Characteristics

The tables below provide information on patient demographics followed by baseline disease characteristics in the two arms.

**Table 8. Patient Demographics in the ITT Population, TIVO-3**

|                     | <b>Tivozanib<br/>(n=175)</b> | <b>Sorafenib<br/>(n=175)</b> |
|---------------------|------------------------------|------------------------------|
| Age in years, n (%) |                              |                              |
| Median (min, max)   | 62 (34, 88)                  | 64 (30, 90)                  |
| <65                 | 98 (56)                      | 95 (54)                      |
| ≥65                 | 77 (44)                      | 80 (46)                      |
| Sex, n (%)          |                              |                              |
| Male                | 126 (72)                     | 128 (73)                     |
| Female              | 49 (28)                      | 47 (27)                      |
| Race, n (%)         |                              |                              |
| White               | 165 (94)                     | 167 (95)                     |
| African American    | 0                            | 2 (1)                        |
| Other               | 3 (2)                        | 2 (1)                        |
| Unknown             | 7 (4)                        | 4 (2)                        |
| Ethnicity, n (%)    |                              |                              |
| Hispanic/Latino     | 10 (6)                       | 10 (6)                       |
| Not Hispanic/Latino | 156 (89)                     | 162 (93)                     |
| Unknown             | 9 (5)                        | 3 (2)                        |

|               | <b>Tivozanib<br/>(n=175)</b> | <b>Sorafenib<br/>(n=175)</b> |
|---------------|------------------------------|------------------------------|
| Region, n (%) |                              |                              |
| North America | 31 (18)                      | 27 (15)                      |
| Europe*       | 144 (82)                     | 148 (85)                     |

Source: dataset ADSL.XPT and CSR Table 5

\*Includes Italy (n=62), Spain (n=55), Poland (n=46), Hungary (n=33), Czech Republic (n=30), United Kingdom (n=29), France (n=13), Germany (n=11), Denmark (n=7), Belgium (n=6)

**Reviewer Comment:** Baseline demographics were similar for both treatment arms. The difference between the 2 arms for each of the baseline characteristics shown above is less than 5%. Most of the patients were White, and the remainder was predominantly “Other” race or race not reported. The majority of patients were male as would be expected for this disease. As in many clinical trials, Blacks were underrepresented. Most patients had an ECOG PS of 0 in both treatment arms.

### Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

Baseline disease characteristics are presented below for patients enrolled in TIVO-3.

**Table 9. Baseline Disease Characteristics in the ITT Population, TIVO-3**

|                                   | <b>Tivozanib<br/>(n=175)</b> | <b>Sorafenib<br/>(n=175)</b> |
|-----------------------------------|------------------------------|------------------------------|
| ECOG PS, n (%)                    |                              |                              |
| 0                                 | 85 (49)                      | 83 (47)                      |
| 1                                 | 88 (50)                      | 84 (48)                      |
| 2                                 | 0                            | 2 (1)                        |
| Missing                           | 2 (1)                        | 6 (3)                        |
| IMDC risk category (eCRF), n (%)  |                              |                              |
| Favorable                         | 26 (15)                      | 35 (20)                      |
| Intermediate                      | 120 (69)                     | 107 (61)                     |
| Poor                              | 29 (17)                      | 33 (19)                      |
| Prior Therapies (eCRF), n (%)     |                              |                              |
| Two VEGFR TKIs                    | 80 (46)                      | 85 (49)                      |
| Checkpoint inhibitor + VEGFR TKI  | 48 (27)                      | 44 (25)                      |
| VEGFR TKI + other systemic agent  | 47 (27)                      | 46 (26)                      |
| Number of metastatic sites, n (%) |                              |                              |
| 1                                 | 13 (7)                       | 25 (14)                      |
| 2                                 | 53 (30)                      | 45 (26)                      |
| 3+                                | 109 (63)                     | 105 (60)                     |
| Baseline Systolic BP, n (%)       |                              |                              |
| ≤140 mmHg                         | 140 (80)                     | 138 (79)                     |
| >140 mmHg                         | 33 (19)                      | 30 (17)                      |
| Missing                           | 2 (1)                        | 7 (4)                        |
| Baseline Diastolic BP, n (%)      |                              |                              |

|          | <b>Tivozanib<br/>(n=175)</b> | <b>Sorafenib<br/>(n=175)</b> |
|----------|------------------------------|------------------------------|
| ≤90 mmHg | 164 (94)                     | 158 (90)                     |
| >90 mmHg | 9 (5)                        | 10 (6)                       |
| Missing  | 2 (1)                        | 7 (4)                        |

Source: dataset ADSL.XPT

**Reviewer Comment:** The FDA notes the relatively low overall use (~25%) of prior checkpoint inhibitors in the TIVO-3 patient population, which is likely a function of the fact that enrollment began in 2016, several years prior to initial FDA approval of nivolumab in the second-line setting, and certainly prior to the subsequent approval of several combination regimens involving checkpoint inhibitors in the first-line metastatic setting. However, the proportion of patients who had received prior checkpoint inhibitor is still higher than that of other recent randomized trials demonstrating clinical benefit of agents in refractory RCC, including axitinib,[17] cabozantinib,[18] and nivolumab.[19] The FDA performed an exploratory analysis of efficacy of tivozanib specifically in those patients who received prior checkpoint inhibitor therapy as those patients might be more similar to the patient receiving their 3<sup>rd</sup> line of treatment in the contemporary treatment setting, and these results are discussed in the efficacy results section below.

Data of stratification factors were collected in both IWRS and eCRF. The concordance and discordance rates between IWRS and eCRF-based stratification data are summarized in Table 10.

**Table 10. Concordance and Discordance of Stratification Data between eCRF and IWRS, TIVO-3**

|                           | <b>Tivozanib<br/>N=175<br/>n (%)</b> | <b>Sorafenib<br/>N=175<br/>n (%)</b> |
|---------------------------|--------------------------------------|--------------------------------------|
| <b>IMDC risk category</b> |                                      |                                      |
| Discordance               | 19 (11)                              | 14 (8)                               |
| Concordance               | 156 (89)                             | 161 (92)                             |
| <b>Prior therapy</b>      |                                      |                                      |
| Discordance               | 26 (15)                              | 20 (11)                              |
| Concordance               | 149 (85)                             | 155 (89)                             |

Source: dataset ADSL.XPT

**Reviewer Comment:** There was no notable difference between arms with respect to discordance rate between the IWRS- and the eCRF-based stratification data. Following the intent-to-treat rule, the primary efficacy analysis used the IWRS-based stratification data. To evaluate the robustness of the results, a sensitivity analysis using eCRF-based stratification data was performed and results are shown in the section of efficacy results.

#### **Treatment Compliance, Concomitant Medications, and Rescue Medication Use**

### Treatment compliance

Treatment compliance was documented by (b) (4) capsule count beginning with Cycle 2. Compliance rates are reflected in Table 21 (Study Drug Exposure in TIVO-3).

### Concomitant medications

Any medication/treatment considered necessary for the patient's welfare, which was not expected to interfere with the evaluation of the study drug, was given at the discretion of the investigator. Prohibited medication/treatment included anti-neoplastic therapy including radiotherapy, herbal preparations/supplements, strong CYP3A4 inducers or inhibitors, and full-dose oral anticoagulants (unless the patient was on a stable dose >2 weeks prior to enrollment).

Generally, the use of concomitant medications was similar between treatment arms. The most frequently ( $\geq 40\%$ ) used concomitant medications in both treatment arms were drugs for peptic ulcer and gastroesophageal reflux disease (60%), opioids (51%), thyroid preparations (48%), other analgesics and antipyretics (48%), antithrombotic agents (43%), and selective calcium channel blocker anti-hypertensives (42%).

### Use of subsequent therapies

Administration of subsequent anti-cancer therapy was summarized in Table 11. Overall, the percentage of patients receiving any subsequent anti-cancer therapy was similar between the two arms (49% vs. 51%). A higher proportion of patients (23%) who were randomized to receive sorafenib received subsequent checkpoint inhibitor compared to patients randomized to receive tivozanib (16%). As this was an open-label study, patients and investigators were aware of the study therapy received by the patient during the trial and subsequent decisions regarding therapy were presumably made with this knowledge.

**Table 11. Summary of Subsequent Anti-Cancer Therapies in the ITT Population, TIVO-3**

|                                                                         | <b>Tivozanib<br/>(N=175)</b> | <b>Sorafenib<br/>(N=175)</b> |
|-------------------------------------------------------------------------|------------------------------|------------------------------|
| # of patients who Received Any Subsequent Anti-Cancer Therapy,<br>n (%) | 85 (49)                      | 89 (51)                      |
| Checkpoint inhibitor                                                    | 28 (16)                      | 41 (23)                      |
| KI                                                                      | 58 (33)                      | 48 (27)                      |
| Other                                                                   | 35 (20)                      | 42 (24)                      |

Source: dataset ADCM.XPT submitted in the final OS package

Abbreviations: KI, kinase inhibitor

**Reviewer Comment:** The FDA notes that a slightly higher overall percentage of progressors who received subsequent anti-cancer therapy on the sorafenib arm received a checkpoint inhibitor vs. those progressors on the tivozanib arm, and although this difference is small, this would actually be expected to weight the OS results in favor of the sorafenib arm as checkpoint

*inhibitors have shown an OS advantage in several lines of therapy in advanced RCC.*

### **Efficacy Results – Primary Endpoint**

Progression-free survival by BIRC was the primary efficacy endpoint of study TIVO-3. PFS was defined as the time from randomization to the first evidence of disease progression or death due to any cause. At the clinical cutoff date of 04 October 2018, 246 PFS events had occurred (123 in each arm), with a median follow-up time for PFS of approximately 18 months on the tivozanib arm and 16 months on the sorafenib arm.

Table 12 presents the results of the primary analysis of PFS by BIRC assessment in the ITT population. A statistically significant improvement in PFS was observed in the tivozanib arm compared to the sorafenib arm with a hazard ratio estimate of 0.73 (95% CI: 0.56, 0.95). The estimate of median PFS was 5.59 months for the tivozanib arm and 3.88 months for the sorafenib arm. The Kaplan-Meier curves of PFS are shown in Figure 2.

**Table 12. Progression-Free Survival Analysis per BIRC Assessment in the ITT Population, TIVO-3**

|                                                                                                                        | <b>Tivozanib<br/>(N=175)</b> | <b>Sorafenib<br/>(N=175)</b> |
|------------------------------------------------------------------------------------------------------------------------|------------------------------|------------------------------|
| Number of events                                                                                                       | 123 (70.3%)                  | 123 (70.3%)                  |
| Progression                                                                                                            | 103 (58.9%)                  | 109 (62.3%)                  |
| Death                                                                                                                  | 20 (11.4%)                   | 14 (8.0%)                    |
| Median (95% CI), in months                                                                                             | 5.59 (4.83, 7.33)            | 3.88 (3.71, 5.55)            |
| HR (95% CI)                                                                                                            | 0.73 (0.56, 0.95)            |                              |
| P-value                                                                                                                | 0.016                        |                              |
| HR was from a Cox proportional hazards model stratified by IMDC risk categories and prior therapy collected from IWRS. |                              |                              |
| P-value was from a log-rank test stratified by IMDC risk categories and prior therapy collected from IWRS.             |                              |                              |
| <i>Source: dataset ADPFS.XPT</i>                                                                                       |                              |                              |

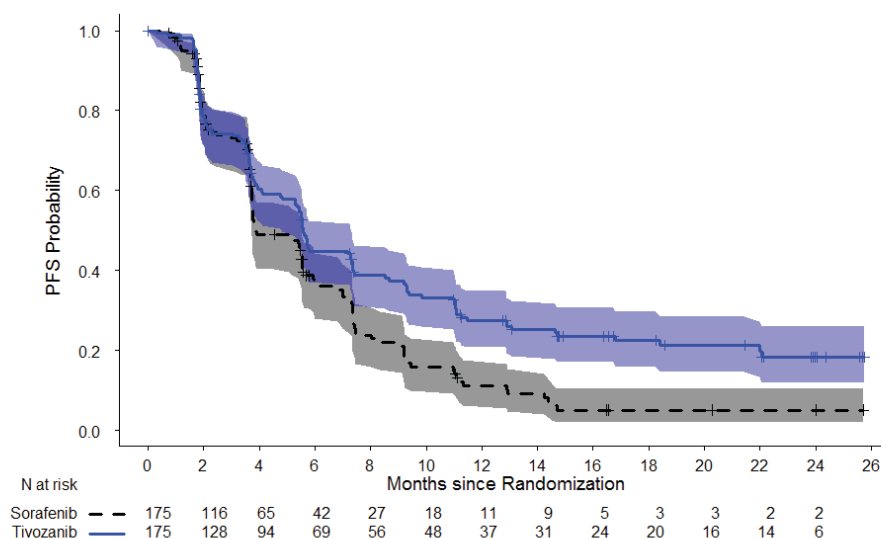


**Figure 2. Kaplan-Meier Curves of PFS per BIRC Assessment, TIVO-3**

Source: dataset ADPFS.XPT

**Reviewer Comment:** Figure 2 shows that separation of the two PFS curves started around the 2<sup>nd</sup> scheduled tumor assessment time point, and the proportional hazards assumption may not hold. A Schoenfeld residual test for non-proportional hazards had a p-value of 0.01 which suggested a departure from the proportional hazards assumption. With that, the review team also estimated PFS rates at 6 months and 12 months as supplementary: the estimates of 6-month PFS rates were 45% vs. 37%, and 12-month PFS rates were 28% vs. 11% for tivozanib arm and sorafenib arm, respectively.

The FDA notes that although the absolute magnitude of improvement in the median PFS between arms was somewhat modest (<2 months), the fact that this improvement was against an active control rather than a placebo or best supportive care arm was reassuring in terms of the efficacy benefit attributed to tivozanib.

In the primary analysis of PFS, 52 patients in each arm have been censored. The reasons for censoring are summarized in Table 13.

**Table 13. Summary of PFS Censoring Reasons, TIVO-3**

|                                                                 | <b>Tivozanib<br/>(N=175)</b> | <b>Sorafenib<br/>(N=175)</b> |
|-----------------------------------------------------------------|------------------------------|------------------------------|
| <b>Number of patients censored, n (%)</b>                       | 52 (30%)                     | 52 (30%)                     |
| <b>Reason for censoring, n (%)</b>                              |                              |                              |
| No post-baseline tumor assessment                               | 5 (3)                        | 9 (5)                        |
| Receiving a new anti-cancer therapy before disease progression* | 18 (10)                      | 27 (15)                      |

|                                                                                                                                                                                                    | <b>Tivozanib<br/>(N=175)</b> | <b>Sorafenib<br/>(N=175)</b> |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------|------------------------------|
| Last tumor assessment without disease progression                                                                                                                                                  | 29 (17)                      | 16 (9)                       |
| <i>Source: Derived from dataset ADPFS.XPT</i>                                                                                                                                                      |                              |                              |
| *In the tivozanib arm, none of these patients were censored occurred within the first 8 weeks. In the sorafenib arm, 13 of the patients were censored within the first 8 weeks after randomization |                              |                              |

**Reviewer Comment:** *It was noted that 31 patients (5 on the tivozanib arm vs. 26 on the sorafenib arm) were censored within 8-weeks post randomization (the first tumor assessment timepoint). Of the patients who were censored within the first 8 weeks after randomization, 0 patients in the tivozanib arm were censored due to receiving a new anti-cancer therapy without evidence of progression of disease, compared to 13 of 26 patients in the sorafenib arm. This suggests informative censoring in the sorafenib arm (e.g., patients or physicians may have believed that sorafenib was an inferior treatment). The impact of this imbalanced early censoring on efficacy results was not clear and thus evaluated in a sensitivity analysis (see the FDA’s sensitivity analyses section).*

#### Sensitivity Analyses of PFS

The applicant has conducted multiple sensitivity analyses for PFS to evaluate the robustness of PFS results (Table 14).

**Table 14. Sensitivity Analyses of PFS Conducted by the Applicant, TIVO-3**

| <b>Sensitivity Analysis</b>                                                                                                                                                                     | <b>Tivozanib<br/>Events/N (%)</b> | <b>Sorafenib<br/>Events/N (%)</b> | <b>Median<br/>(months)<br/>Tivozanib vs.<br/>Sorafenib</b> | <b>HR<br/>(95% CI)</b> |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------|-----------------------------------|------------------------------------------------------------|------------------------|
| 1. PFS per INV assessment                                                                                                                                                                       | 124/175 (71)                      | 129/175 (74)                      | 5.98 vs. 5.39                                              | 0.62<br>(0.48, 0.80)   |
| 2. PFS per INV assessment including clinical PDs in the ITT population                                                                                                                          | 125/175 (71)                      | 133/175 (76)                      | 5.98 vs. 5.39                                              | 0.61<br>(0.47, 0.79)   |
| 3. PFS per BIRC in the ITT population, considering the following as events: (1) initiation of a new anti-tumor treatment; (2) events after 2+ missed assessments                                | 141/175 (81)                      | 150/175 (86)                      | 5.55 vs. 3.75                                              | 0.66<br>(0.52, 0.84)   |
| 4. PFS per BIRC in the ITT population, considering the following as events: (1) initiation of a new anti-tumor treatment; (2) events after 2+ missed assessments; (3) treatment discontinuation | 149/175 (85)                      | 166/175 (95)                      | 4.76 vs. 3.68                                              | 0.61<br>(0.48, 0.77)   |
| 5. PFS per BIRC in the ITT population, backdate any PD events after missing or NE assessment to                                                                                                 | 123/175 (70)                      | 124/175 (71)                      | 5.59 vs. 3.88                                              | 0.72<br>(0.56, 0.94)   |

| Sensitivity Analysis                                                                              | Tivozanib<br>Events/N (%) | Sorafenib<br>Events/N (%) | Median<br>(months)<br>Tivozanib vs.<br>Sorafenib | HR<br>(95% CI)       |
|---------------------------------------------------------------------------------------------------|---------------------------|---------------------------|--------------------------------------------------|----------------------|
| the date of first missed assessment or NE preceding the PD                                        |                           |                           |                                                  |                      |
| 6. PFS per BIRC in the ITT population, stratification factor data from eCRF                       | 123/175 (70)              | 123/175 (70)              | 5.59 vs. 3.88                                    | 0.71<br>(0.55, 0.93) |
| 7. PFS per BIRC in the ITT population, unstratified analysis                                      | 123/175 (70)              | 123/175 (70)              | 5.59 vs. 3.88                                    | 0.67<br>(0.52, 0.86) |
| 8. PFS per BIRC in the SAF population, stratification factor data from eCRF                       | 123/173 (71)              | 122/170 (72)              | 5.59 vs. 3.91                                    | 0.74<br>(0.57, 0.96) |
| INV=Investigator; NE=Non-Evaluable; SAF=Safety; ITT=Intent to Treat<br>Source: datasets ADPFS.XPT |                           |                           |                                                  |                      |

**Reviewer Comments:** Results of the sponsor’s sensitivity analyses support the primary PFS efficacy findings.

FDA’s Analysis of Discordance between BIRC and INV Assessment of Disease Progression

Per the study design, disease status was assessed by both BIRC and INV. The primary PFS analysis was based on the BIRC assessment, with the INV-based PFS as a supportive analysis. Discordance rates between BIRC and INV assessments are shown in Table 15. The discordance rate in terms of PFS status (event vs. censoring) was 19% in the tivozanib arm and 14% in the sorafenib arm. The discordance rates are similar between arms.

**Table 15. Discordance and Concordance Rates of PFS Event Status between BIRC and INV Assessments, TIVO-3**

|          | Tivozanib<br>(n=175) |               | Sorafenib<br>(n=175) |               |
|----------|----------------------|---------------|----------------------|---------------|
|          | BIRC Events          | BIRC censored | BIRC Events          | BIRC censored |
| INV      |                      |               |                      |               |
| Events   | 107 (61%)            | 17 (10%)      | 114 (65%)            | 15 (9%)       |
| Censored | 16 (9%)              | 35 (20%)      | 9 (5%)               | 37 (21%)      |

Source: datasets ADPFS.XPT

FDA’s sensitivity analyses of PFS

1. Death post study discontinuation: Three patients on the tivozanib arm died within 16 weeks post randomization, but the death occurred after study discontinuation and these 3 patients were not counted as PFS events in the primary PFS analysis. In this sensitivity analysis, the 3 patients were considered as events at the time of death, and the estimate of hazard ratio was 0.75 (95% CI: 0.58, 0.97).
2. Early censoring: As shown in Table 16, more patients randomized to the sorafenib arm were censored within 8 weeks post randomization. To evaluate the impact of imbalance

in the early censoring rates (3% vs. 15%), we performed a resampling analysis of PFS per BIRC assessment by imputing early censored patients (patients censored at a timepoint  $\leq 8$  weeks from randomization) using PFS data randomly sampled from patients censored or progressed after 8 weeks and repeated this procedure for 1000 times. The median of HR estimates based on the 1000 samples was 0.71 (95% CI: 0.55, 0.90) and the median of PFS median difference between arms was 1.7 months.

**Table 16. Censoring and Event Distribution by Time, TIVO-3**

|                                                             | <b>Tivozanib<br/>(n=175)</b> | <b>Sorafenib<br/>(n=175)</b> |
|-------------------------------------------------------------|------------------------------|------------------------------|
| <b>Censored <math>\leq 8</math> weeks</b>                   | 5 (3)                        | 26 (15)                      |
| <b>Events occurred <math>\leq 8</math> weeks</b>            | 22 (13)                      | 17 (10)                      |
| <b>Censored or events occurred <math>&gt;8</math> weeks</b> | 148 (85)                     | 132 (75)                     |

Source: ADPFS.XPT

- Interval censoring: The observed benefit of tivozanib in median PFS was modest which is less than the imaging assessment interval (every 8 weeks). A post-hoc interval censoring analysis was conducted to explore the robustness of the primary analysis results of PFS per BIRC assessment with respect to the imaging assessment interval. In this analysis the estimate of stratified hazard ratio was 0.70 (95% CI: 0.54, 0.92) and the estimate of median PFS was 5.32 months (95% CI: 3.78, 5.75) and 3.75 months (95% CI: 3.22, 5.09) for the tivozanib arm and the sorafenib arm, respectively.

**Reviewer Comment:** Results of the sensitivity analyses support the primary PFS efficacy findings (HR 0.73 [primary analysis] vs. 0.75 [sensitivity analysis 1] vs. 0.71 [sensitivity analysis 2] vs. 0.70 [sensitivity analysis 3]).

Exploratory subgroup analyses of PFS by demographics and baseline disease characteristics are presented in Table 17.

**Table 17. Subgroup Analyses of PFS-BIRC per Baseline Characteristics, TIVO-3**

|             | Number of Events/Total N<br>(% of Patients with Event) |              | Median (months) |           | HR (95% CI) <sup>1</sup> |
|-------------|--------------------------------------------------------|--------------|-----------------|-----------|--------------------------|
|             | Tivozanib                                              | Sorafenib    | Tivozanib       | Sorafenib |                          |
| <b>Age</b>  |                                                        |              |                 |           |                          |
| <65         | 69/98 (70)                                             | 68/95 (72)   | 5.6             | 3.7       | 0.75 (0.53, 1.05)        |
| $\geq 65$   | 54/77 (70)                                             | 55/80 (69)   | 5.8             | 5.6       | 0.59 (0.40, 0.87)        |
| <b>Sex</b>  |                                                        |              |                 |           |                          |
| Male        | 87/126 (69)                                            | 93/128 (73)  | 5.7             | 5.2       | 0.64 (0.48, 0.86)        |
| Female      | 36/49 (73)                                             | 30/47 (64)   | 5.4             | 3.8       | 0.72 (0.44, 1.19)        |
| <b>Race</b> |                                                        |              |                 |           |                          |
| White       | 116/165 (70)                                           | 118/167 (71) | 5.6             | 3.9       | 0.67 (0.51, 0.87)        |

|                                                                                                       | Number of Events/Total N<br>(% of Patients with Event) |              | Median (months) |           | HR (95% CI) <sup>1</sup> |
|-------------------------------------------------------------------------------------------------------|--------------------------------------------------------|--------------|-----------------|-----------|--------------------------|
|                                                                                                       | Tivozanib                                              | Sorafenib    | Tivozanib       | Sorafenib |                          |
| Non-White                                                                                             | 7/10 (70)                                              | 5/8 (62)     | 3.8             | 2.8       | 0.75 (0.23, 2.48)        |
| <b>Region</b>                                                                                         |                                                        |              |                 |           |                          |
| North America                                                                                         | 17/31 (55)                                             | 9/27 (33)    | 7.3             | 3.9       | 0.71 (0.31, 1.60)        |
| European Union                                                                                        | 106/144 (74)                                           | 114/148 (77) | 5.6             | 3.9       | 0.69 (0.53, 0.90)        |
| <b>ECOG PS</b>                                                                                        |                                                        |              |                 |           |                          |
| 0                                                                                                     | 55/85 (65)                                             | 60/83 (72)   | 7.4             | 3.8       | 0.54 (0.37, 0.78)        |
| 1                                                                                                     | 68/88 (77)                                             | 61/84 (73)   | 4.8             | 5.1       | 0.88 (0.62, 1.25)        |
| <b>IMDC Risk (eCRF)</b>                                                                               |                                                        |              |                 |           |                          |
| Favorable                                                                                             | 16/26 (62)                                             | 21/35 (60)   | 11.1            | 6.8       | 0.43 (0.22, 0.83)        |
| Intermediate                                                                                          | 81/120 (67)                                            | 75/107 (70)  | 5.6             | 5.4       | 0.70 (0.51, 0.95)        |
| Poor                                                                                                  | 26/29 (90)                                             | 27/33 (82)   | 2.1             | 3.7       | 1.12 (0.64, 1.97)        |
| <b>Prior therapy (eCRF)</b>                                                                           |                                                        |              |                 |           |                          |
| Two VEGFR TKIs                                                                                        | 57/80 (71)                                             | 67/85 (79)   | 5.3             | 3.7       | 0.62 (0.43, 0.89)        |
| CPI + TKI                                                                                             | 30/48 (62)                                             | 23/44 (52)   | 7.3             | 5.9       | 0.67 (0.39, 1.16)        |
| TKI + other                                                                                           | 36/47 (77)                                             | 33/46 (72)   | 5.8             | 7.3       | 0.83 (0.52, 1.34)        |
| <b>Number of metastatic sites</b>                                                                     |                                                        |              |                 |           |                          |
| 1                                                                                                     | 11/13 (85)                                             | 19/25 (76)   | 2.3             | 3.7       | 0.90 (0.42, 1.91)        |
| 2+                                                                                                    | 112/162 (69)                                           | 104/150 (69) | 5.7             | 5.1       | 0.68 (0.52, 0.89)        |
| <b>Baseline Diastolic and Systolic BP</b>                                                             |                                                        |              |                 |           |                          |
| sBP>140mmHg<br>or dBP>90mmHg                                                                          | 25/34 (74)                                             | 25/34 (74)   | 5.6             | 3.9       | 0.67 (0.38, 1.17)        |
| sBP≤140mmHg<br>and dBP≤90mmHg                                                                         | 98/139 (70)                                            | 96/134 (72)  | 5.6             | 3.9       | 0.69 (0.51, 0.91)        |
| <sup>1</sup> HR was estimated from an unstratified Cox proportional hazards model<br>Source ADPFS.XPT |                                                        |              |                 |           |                          |

**Reviewer Comments:**

*All of the subgroup analyses presented are considered exploratory or hypothesis-generating and no formal statistical inference may be drawn.*

*No apparent outliers were observed in the subgroup analyses. In the subgroup of patients with poor IMDC risk level (n=62), the point estimate of hazard ratio is 1.12; however, the sample size is small and the wide confidence interval includes 1.*

*The FDA notes that the patients who received prior checkpoint inhibitor therapy appear to derive consistent PFS benefit compared to those patients who did not receive prior checkpoint inhibitor therapy. While the number of patients who received prior checkpoint inhibitor is low, the results of this subgroup analysis may be considered supportive data with clinical relevance. Since the approvals of frontline combination regimens containing checkpoint inhibitor (2018-2020) by FDA, data to support use of specific second- or third-line agents in the new treatment paradigm is limited. The PFS-BIRC HR is similar to that of the overall population (0.67 95% CI, 0.39, 1.16]), reassuring the review team that tivozanib will have a role in the context of contemporary regimens.*

### Efficacy Results – Secondary and other relevant endpoints

The study statistical analysis plan did not pre-specify any multiplicity adjustment method for analyses of secondary endpoints. Although an O'Brien-Fleming boundary was used for alpha allocation at the OS interim and final analyses, no alpha was pre-specified to be allocated to OS after the primary endpoint PFS reached statistical significance. Therefore, analyses of all secondary endpoints are considered exploratory.

#### Overall Survival

Overall survival was one of the secondary endpoints. In the initial SAP, only one interim analysis was planned for overall survival to be conducted at the time of primary PFS analysis. After the primary PFS analysis was conducted, the SAP was amended several times, and the final version of SAP included two interim and one final analyses of OS. The first OS interim analysis was performed at the time of primary PFS analysis and results numerically favored sorafenib with a hazard ratio estimate of 1.12 (95% CI: 0.40, 1.51) based on 183 death events. The second interim analysis was conducted after all patients were on study for at least 2 years. At the second interim analysis (cutoff date: August 15, 2019), 227 death events occurred, and the hazard ratio estimate was 0.99 (95% CI: 0.76, 1.29) which numerically favored tivozanib. The final analysis was performed based on a data cutoff date of May 1<sup>st</sup>, 2020. As of that cutoff date, 251 death events have occurred. The results of the OS final analysis are summarized in Table 18 and the Kaplan-Meier plot is provided in Figure 3. The median follow-up time for overall survival was 38 months on the tivozanib arm and 40 months on the sorafenib arm as of the data cutoff date for the final analysis.

**Table 18. Results of the Final Overall Survival Analysis, TIVO-3**

|                                                                                                                   | <b>Tivozanib<br/>(N=175)</b> | <b>Sorafenib<br/>(N=175)</b> |
|-------------------------------------------------------------------------------------------------------------------|------------------------------|------------------------------|
| OS events, n (%)                                                                                                  | 125 (71.4)                   | 126 (72.0)                   |
| Median (95% CI), in months                                                                                        | 16.39 (13.44, 21.95)         | 19.15 (14.92, 24.21)         |
| HR (95% CI)                                                                                                       | 0.97 (0.75, 1.24)            |                              |
| HR was estimated from a Cox proportional hazards model stratified by IMDC risk category and prior therapy         |                              |                              |
| <i>Source: dataset ADTTE.XPT and Information request response from the Applicant on June 5<sup>th</sup>, 2020</i> |                              |                              |

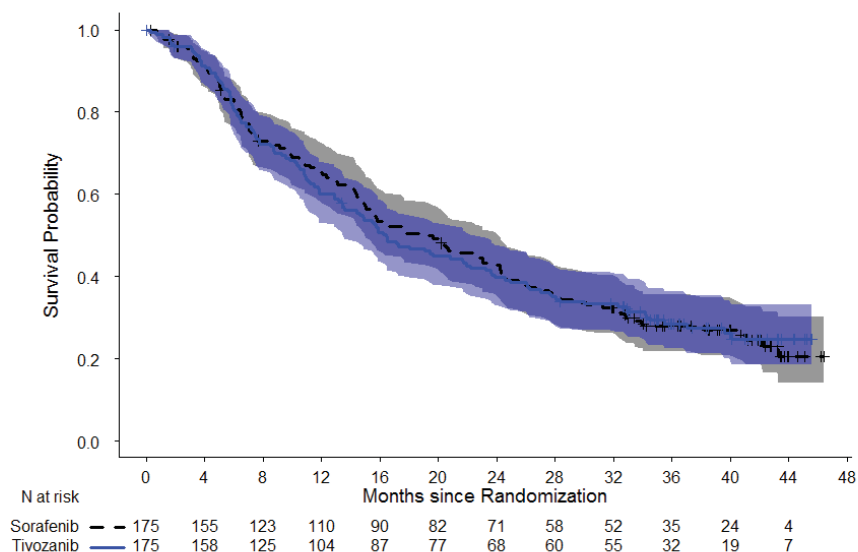


**Figure 3. Kaplan-Meier Curves of Overall Survival, TIVO-3**

Source: dataset ADTTE.XPT

**Reviewer Comments:**

*Per the applicant’s communication with the FDA on 22 May 2020, the applicant found the actual date of death for one patient who was censored in the applicant’s OS final analysis due to uncertainty of the death date at the time of the database lock. The review team used the actual death date of that patient in the final OS analysis as presented in Table 17 and Figure 3.*

*As of the data cutoff date for the final OS analysis, 99 patients were censored, of whom 82 patients (46 tivozanib vs. 36 sorafenib) were still on study and under long-term follow-up for survival. All but one patient was censored within 2 months before the cutoff date for the final OS analysis. Therefore, the censoring distribution is acceptable.*

*The review team noted that the point estimate of OS hazard ratio is close to 1 and the median estimate of the tivozanib arm is approximately 3 months shorter than that of the sorafenib arm. Therefore, possible detrimental effect of tivozanib on OS is a concern. Given that the median is only one timepoint on the survival curve and the difference at one timepoint may not reflect the overall curves, the review team also conducted a post-hoc exploratory analysis using restricted mean survival time (RMST) method to estimate the treatment effect. Using a cutoff time at month 44 for RMST estimation, the difference of RMST estimate between tivozanib and sorafenib is -0.4 months (95% CI: -3.7, 2.9). To explore RMST estimates at different cutoff timepoints, RMST difference between the two arms by cutoff timepoint is shown in Figure 2. Overall, the point estimates of RMST differences using various cutoffs are between -0.51 and 0.02 months (negative values favor sorafenib) and the confidence intervals are wide. Given that the Kaplan-Meier plot shows overlapping survival curves, a hazard ratio less than one in favor of*

the tivozanib arm, and a small difference of OS between the two arms observed using the RMST approach, it appears that tivozanib does not have an apparent detrimental effect on OS.

The review team also performed additional sensitivity analyses on final overall survival. The unstratified OS analysis had a hazard ratio point estimate of 1.003 (95% CI: 0.78, 1.28) and the OS analysis stratified by stratification factors data collected on eCRFs had a hazard ratio point estimate of 0.97 (95% CI: 0.75, 1.25). Results are similar to the primary findings of OS.

The FDA also notes that the overall survival analysis of tivozanib are vs. sorafenib, which represents an active therapeutic option in this setting. The phase 3 trial of sorafenib vs. placebo in patients with advanced RCC that led to FDA approval based on PFS later reported an OS HR estimate of 0.88 (95%CI: 0.74, 1.04), favoring sorafenib, despite crossover.[20] Thus, these results are interpreted through that perspective as well.

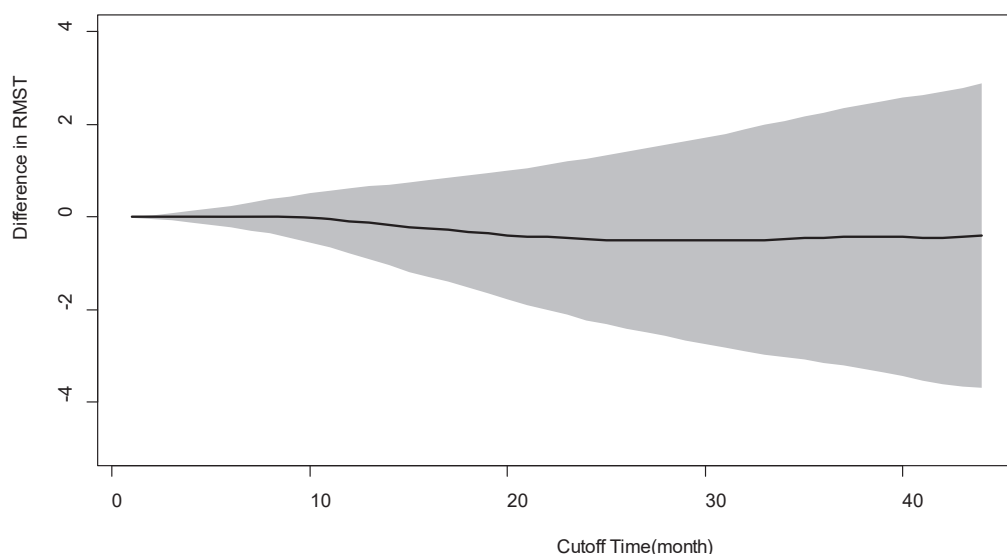


**Figure 4. Difference in RMST of Overall Survival Between Arms by Cutoff Time, TIVO-3**

Source: dataset ADTTE.XPT

### OS subgroup analyses

Exploratory subgroup analyses of OS by demographics and baseline disease characteristics are presented in Table 19.

**Table 19. Subgroup Analyses of Final Overall Survival per Baseline Characteristics, TIVO-3**

|            | Number of Events/Total N<br>(% of Patients with Event) |            | Median (months) |           | HR (95% CI) <sup>1</sup> |
|------------|--------------------------------------------------------|------------|-----------------|-----------|--------------------------|
|            | Tivozanib                                              | Sorafenib  | Tivozanib       | Sorafenib |                          |
| <b>Age</b> |                                                        |            |                 |           |                          |
| <65        | 73/98 (74)                                             | 72/95 (76) | 15.9            | 16.3      | 1.01 (0.73, 1.41)        |
| ≥65        | 52/77 (68)                                             | 54/80 (67) | 17.6            | 20.6      | 1.00 (0.68, 1.46)        |

|                                                                                                       | Number of Events/Total N<br>(% of Patients with Event) |              | Median (months) |           | HR (95% CI) <sup>1</sup> |
|-------------------------------------------------------------------------------------------------------|--------------------------------------------------------|--------------|-----------------|-----------|--------------------------|
|                                                                                                       | Tivozanib                                              | Sorafenib    | Tivozanib       | Sorafenib |                          |
| <b>Sex</b>                                                                                            |                                                        |              |                 |           |                          |
| Male                                                                                                  | 93/126 (74)                                            | 89/128 (70)  | 17.1            | 20.5      | 1.09 (0.82, 1.46)        |
| Female                                                                                                | 32/49 (65)                                             | 37/47 (79)   | 14.6            | 14.3      | 0.79 (0.49, 1.28)        |
| <b>Race</b>                                                                                           |                                                        |              |                 |           |                          |
| White                                                                                                 | 118/165 (72)                                           | 119/167 (71) | 16.4            | 19.6      | 1.02 (0.79, 1.32)        |
| Non-White                                                                                             | 7/10 (70)                                              | 7/8 (87)     | 19.0            | 13.5      | 0.65 (0.22, 1.90)        |
| <b>Region</b>                                                                                         |                                                        |              |                 |           |                          |
| North America                                                                                         | 17/31 (55)                                             | 17/27 (63)   | 32.3            | 24.2      | 0.85 (0.43, 1.66)        |
| European Union                                                                                        | 108/144 (75)                                           | 109/148 (74) | 15.7            | 16.3      | 1.03 (0.79, 1.35)        |
| <b>ECOG PS</b>                                                                                        |                                                        |              |                 |           |                          |
| 0                                                                                                     | 54/85 (64)                                             | 55/83 (66)   | 23.9            | 24.3      | 0.95 (0.66, 1.39)        |
| 1                                                                                                     | 70/88 (80)                                             | 66/84 (79)   | 11.8            | 14.3      | 1.01 (0.72, 1.41)        |
| <b>IMDC Risk (eCRF)</b>                                                                               |                                                        |              |                 |           |                          |
| Favorable                                                                                             | 11/26 (42)                                             | 19/35 (54)   | NR              | 32.9      | 0.70 (0.33, 1.48)        |
| Intermediate                                                                                          | 87/120 (73)                                            | 76/107 (71)  | 15.4            | 19.7      | 1.12 (0.83, 1.53)        |
| Poor                                                                                                  | 27/29 (93)                                             | 31/33 (94)   | 9.6             | 6.6       | 0.67 (0.40, 1.13)        |
| <b>Prior therapy (eCRF)</b>                                                                           |                                                        |              |                 |           |                          |
| Two VEGFR TKIs                                                                                        | 56/80 (70)                                             | 60/85 (71)   | 14.8            | 15.4      | 0.93 (0.65, 1.34)        |
| CPI + TKI                                                                                             | 32/48 (67)                                             | 31/44 (70)   | 19.1            | 24.2      | 0.99 (0.61, 1.63)        |
| TKI + other systemic agent                                                                            | 37/47 (79)                                             | 35/46 (76)   | 18.0            | 21.8      | 1.14 (0.72, 1.82)        |
| <b>Number of metastatic sites</b>                                                                     |                                                        |              |                 |           |                          |
| 1                                                                                                     | 10/12 (83)                                             | 16/23 (70)   | 12.3            | 29.3      | 1.77 (0.80, 3.94)        |
| 2+                                                                                                    | 115/163 (71)                                           | 110/152 (72) | 16.5            | 16.2      | 0.95 (0.73, 1.23)        |
| <b>Baseline Systolic and Diastolic BP</b>                                                             |                                                        |              |                 |           |                          |
| sBP>140 or dBP>90                                                                                     | 27/34 (79)                                             | 20/34 (59)   | 21.4            | 24.4      | 1.54 (0.86, 2.76)        |
| sBP≤140 and dBP≤90                                                                                    | 97/139 (70)                                            | 102/134 (76) | 15.7            | 15.8      | 0.88 (0.67, 1.16)        |
| <sup>1</sup> HR was estimated from an unstratified Cox proportional hazards model<br>Source ADTTE.XPT |                                                        |              |                 |           |                          |

**Reviewer Comments:** All of the subgroup analyses presented are considered exploratory or hypothesis generating and no formal statistical inference may be drawn.

The point estimate of hazard ratio was around 1 in most of the subgroups analyzed. In the subgroup of patients with one metastatic site and subgroup with high blood pressure at baseline had their point estimate of hazard ratio as 1.77 and 1.54, respectively. However, the sample size in both subgroups is small and the wide confidence interval includes 1.

FDA sent an Information Request to the sponsor for potential explanations for the OS HR of 1.54 among patients with baseline high sBP or dBP. The sponsor emphasized the possibility of small random sample variability. The sponsor also conducted additional analyses that suggested that

*there is no negative effect on OS for tivozanib in patients who are hypertensive at baseline. “There may be a positive effect for sorafenib, but the data available are not sufficient to make conclusions. However, the use of subsequent therapy may be a possible confounding variable.” The FDA also notes the hazard ratio and point estimate for patients with prior CPI, which appeared similar to the overall population results. This is also reassuring and useful data as combination CPI is currently the standard initial therapy in the frontline. Furthermore, as noted in the Reviewer comment pertaining to Table 11, the number of patients who received a checkpoint inhibitor was higher in the sorafenib arm compared to the tivozanib arm, which would be expected to weight the efficacy results in favor of the sorafenib arm.*

### Objective Response Rate

The objective response rate included confirmed complete response rate and confirmed partial response based on RECIST v1.1 per BIRC assessment and was calculated in the intent-to-treatment population. As shown in Table 20, the tivozanib arm had an ORR rate per BIRC of 18% and the sorafenib arm had a rate of 8%. All responders had partial responses. The median duration of response was not reached in the tivozanib arm and 5.7 months in the sorafenib arm.

**Table 20. Objective Response Rate and Duration of Response Per BIRC in the ITT Population, TIVO-3**

|                                                          | <b>Tivozanib<br/>(n=175)</b> | <b>Sorafenib<br/>(n=175)</b> |
|----------------------------------------------------------|------------------------------|------------------------------|
| <b>Best overall response, n (%)</b>                      |                              |                              |
| Complete Response                                        | 0                            | 0                            |
| Partial Response                                         | 31 (18)                      | 14 (8)                       |
| Stable Disease                                           | 94 (54)                      | 99 (57)                      |
| Progressive Disease                                      | 37 (21)                      | 32 (18)                      |
| Not Evaluable/Not Assessed/Not Applicable                | 10 (6)                       | 30 (17)                      |
|                                                          |                              |                              |
| <b>Objective Response Rate, n (%)</b>                    | 31 (18)                      | 14 (8)                       |
| (95% CI)                                                 | (12, 24)                     | (4, 13)                      |
| <b>Duration of Response</b>                              |                              |                              |
| # of Responders                                          | 31                           | 14                           |
| # of Events, n (%)                                       | 10 (32)                      | 9 (64)                       |
| Median (95% CI), in months                               | NE (9.8, NE)                 | 5.7 (5.6, NE)                |
| # of patients with ongoing response at one year (%)      | 11 (35)                      | 6 (43)                       |
| NE=Not Estimable<br>Source: datasets ADRS.XPT, ADTTE.XPT |                              |                              |

### **Reviewer’s comments:**

*Per the investigator assessment, the confirmed ORR (PR only) was 22% and 11% in the tivozanib arm and the sorafenib arm, respectively. The discordance rate of ORR between BIRC and*

*investigator assessment was 9% in the tivozanib arm and 5% in the sorafenib arm. Investigators tended to call more responders in both arms. The antitumor activity of tivozanib is supportive data for the efficacy of this agent.*

### **Dose/Dose Response**

Not applicable. All patients were started at the FDA-approved recommended dose for patients with RCC in the product label.

### **Durability of Response**

See information provided above concerning the response rate and duration of response. Duration of response is difficult to interpret in a small number of patients.

### **Persistence of Effect**

See information provided above concerning duration of response and progression-free survival.

### **Efficacy Results – Secondary or exploratory COA (PRO) endpoints**

The applicant did not collect any PRO data in TIVO-3. See Section 8.2.6 for FDA's review on PRO data collected in TIVO-1, which was a randomized trial with the same treatment regimens administered in TIVO-3, tivozanib versus sorafenib.

### **Additional Analyses Conducted on the Individual Trial**

No additional analyses were conducted.

#### **8.1.3 TIVO-1 (AV-951-09-301)**

The Applicant submitted supportive efficacy data of tivozanib in patients with KI-naïve advanced RCC based on data from a single clinical trial (TIVO-1). FDA conducted a full review of this data in NDA 204408. These results were also presented and discussed at ODAC in May 2013 (see Section 3.2 of this review).

TIVO-1 was a multicenter trial that randomized 517 patients with advanced RCC without prior therapy or having received one prior systemic cytokine therapy. Patients were randomized to receive tivozanib versus sorafenib. The primary endpoint was PFS according to BIRC.

The study met the primary endpoint: PFS HR 0.80 (95% CI: 0.64, 0.99), median difference of 2.8 months (11.9 vs. 9.1 months). The primary analysis used a stratified analysis based on number of prior treatments and number of metastatic sites. The reasons for censoring of patients were generally balanced between the two treatment arms.

Overall survival was the first of the secondary endpoints. The final OS analysis used data

collected through August 27, 2012 when all patients had been followed for a minimum of two years and when there were 219 OS events. This analysis demonstrated a decrement in OS of tivozanib as compared to sorafenib that was not statistically significant with a hazard ratio of 1.25 (95% CI: 0.95, 1.62; p=0.11). While the median difference in survival was two weeks, the review team stated that this estimate might not be reliable since few patients had died (118 patients in the tivozanib arm vs. 101 in the sorafenib arm) and the survival time estimate at the fortieth percentile was four months longer in the sorafenib arm.

The review team at the time concluded that the OS analysis was greatly confounded by a significant design flaw, which was one-way crossover: patients who progressed on sorafenib could receive tivozanib through an extension study (AV-951-09-902), but patients who progressed on tivozanib were not given any similar opportunity to receive second-line therapy. Therefore, a differential use of subsequent targeted therapies in patients with disease progression between the two arms was thought to have biased the results for overall survival. One hundred and fifty-four (60%) patients randomized to sorafenib received targeted therapy, the majority having crossed over to tivozanib, as compared to only 31 (12%) patients from the tivozanib arm. While the assessment of PFS was a true comparison of the tivozanib to sorafenib, the analysis of OS was thought to essentially be a comparison of tivozanib against sequential targeted therapies. Thus, the overall survival results were considered not interpretable by FDA.

The applicant presented several justifications to support their contention that the decrement in overall survival was due to differential treatment of patients following disease progression. This included the fact that the apparent toxicity of tivozanib was similar or less than sorafenib (similar rates of adverse events leading to death), the absolute overall survival for the tivozanib arm in this trial was similar to that of previous trials, and that there was not a decrement in overall survival in patients receiving tivozanib post progression. While many of the Applicant's arguments were considered plausible, they were all post hoc and were thought to not completely rule out the possibility that either sorafenib was a superior drug when it comes to overall survival or that there was some aspect of tivozanib that accelerates demise following disease progression.

#### **8.1.4 Extension Study (AV-951-09-301)**

As noted in Section 8.1.3, patients who progressed on sorafenib could receive tivozanib through an extension study (AV-951-09-301) (see also Table 4). The extension study was a single-arm study with no primary efficacy endpoint (N=161). The Applicant provided investigator-assessed efficacy results: ORR of 18%, PFS of 11 months, OS of 21.6 months. These results represent exploratory efficacy data in patients who received second-line tivozanib. Since the extension study was never designed to assess efficacy and time-to-event endpoints are uninterpretable in single-arm trials, FDA does not consider these results demonstration of substantial evidence of effectiveness of tivozanib for the second-line indication.

The sponsor submitted this data as supportive efficacy data as justification for the proposed indication statement of “patients with relapsed or refractory RCC.” As TIVO-3 did not enroll patients with RCC whose disease had progressed on only 1 prior systemic regimen, FDA revised the sponsor’s proposed indication for the approval from “patients with relapsed or refractory RCC” to “patients with relapsed or refractory RCC with disease progression on or after two or more prior lines of therapy.”

### **8.1.5 Integrated Review of Effectiveness**

In NDA 212904, efficacy was assessed based on data from a single clinical trial (TIVO-3) reviewed in Sections 8.1.1 and 8.1.2.

#### **Primary Endpoints**

Not applicable. In NDA 212904, efficacy was assessed based on data from a single clinical trial (TIVO-3) reviewed in Sections 8.1.1 and 8.1.2.

#### **Secondary and Other Endpoints**

Not applicable. In NDA 212904, efficacy was assessed based on data from a single clinical trial (TIVO-3) reviewed in Sections 8.1.1 and 8.1.2.

#### **Subpopulations**

Not applicable. In NDA 212904, efficacy was assessed based on data from a single clinical trial (TIVO-3) reviewed in Sections 8.1.1 and 8.1.2.

#### **Conducting a pooled subgroup analysis**

Not applicable. In NDA 212904, efficacy was assessed based on data from a single clinical trial (TIVO-3) reviewed in Sections 8.1.1 and 8.1.2.

#### **Additional Efficacy Considerations**

Not applicable. In NDA 212904, efficacy was assessed based on data from a single clinical trial (TIVO-3) reviewed in Sections 8.1.1 and 8.1.2.

### **8.1.6 Integrated Assessment of Effectiveness**

The efficacy of tivozanib in patients with histologically or cytologically confirmed RCC that has progressed on 2 or 3 prior systemic regimens is supported by a single, multi-national, open-label randomized controlled clinical study, TIVO-3. The primary endpoint of BIRC assessed PFS was prolonged in patients randomized to receive tivozanib (median estimate 5.59 months)

compared to sorafenib (median estimate 3.88 months). The FDA agrees that the observed benefit on PFS was both statistically significant (HR estimate 0.73, p-value 0.016) and clinically meaningful considering that the comparison is between tivozanib and an active control arm, sorafenib. Sorafenib's activity in this disease setting over placebo has been demonstrated in a randomized controlled trial.[4] Results of sensitivity analyses and subgroup analyses of BIRC-PFS supported the primary findings.

Survival curves of the two arms are close to each other with a hazard ratio of 0.97 (95% CI: 0.75, 1.24). No apparent detrimental effect of tivozanib on survival was observed. Results of ORR are supportive, with PRs reported in 22% vs. 11% (tivozanib vs. sorafenib, respectively).

Tivozanib had previously been evaluated in TIVO-1, which randomized patients with treatment-naïve advanced RCC to receive tivozanib versus sorafenib. Although TIVO-1 met its primary endpoint, a trend towards a detrimental effect on survival was observed with tivozanib. An ODAC vote on May 2, 2013 was 13:1 no:yes in response to the question "Has the Applicant demonstrated a favorable benefit to risk evaluation for the treatment of renal cell carcinoma in an adequate and well-controlled trial?". Voting members cited concerns that included the observed decrement in the HR estimate for OS and confounding factors in the trial design.

Despite the negative ODAC vote for tivozanib in the KI-naïve RCC setting and the subsequent CR letter issued on June 6, 2013 for tivozanib based on review of TIVO-1, the review team felt that the totality of the TIVO-3 data warranted an approval in this case given the PFS advantage, supportive ORR, acceptable safety for the intended population, and the HR for OS that ultimately did not demonstrate a decrement in patients who were required to have had previous treatment with 2 prior lines of therapy. Although the Applicant had requested an indication that included all patients with advanced renal cell carcinoma based also on extension study AV-951-09-301, the FDA review team granted an indication that reflected only the TIVO-3 enrolled population, i.e. patients who progressed on two prior lines of therapy.

In conclusion, the efficacy of tivozanib for patients with RCC that has progressed on 2 or 3 prior systemic regimens is supported by the result of the primary endpoint, secondary endpoints, subgroup analyses, and sensitivity analyses. The results supported by scientific knowledge about the effectiveness of other drugs in the same pharmacologic class, is adequate demonstration of substantial evidence of effectiveness of tivozanib, as stated by the *Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products* Draft Guidance for Industry (December 2019).[21] The submitted evidence meets the statutory evidentiary standard for regular approval of tivozanib for this indication.

## 8.2 Review of Safety

### 8.2.1 Safety Review Approach

The focus of the safety review for this application is the 173 patients treated with tivozanib in the phase 3 TIVO-3 Study. The data cutoff for the original submission was August 15, 2019, and

May 1, 2020, for the Safety Update. Supportive safety and tolerability data was obtained from 5 other trials as described in the table below, for a total of 1008 patients with advanced RCC who received tivozanib monotherapy at the proposed dose and schedule.

## 8.2.2 Review of the Safety Database

### Overall Exposure

The safety of tivozanib has been evaluated in 15 Sponsor-initiated studies:

- Tivozanib monotherapy in patients with RCC at the proposed dose and schedule (the 6 studies outlined in the table below)
- Tivozanib monotherapy for solid tumors (3 studies)
- Tivozanib in combination with other therapy for various solid tumors (6 studies)

Data from patients with non-RCC tumors or who received combination therapy are not included in the clinical safety portion of this review.

**Table 21. Tivozanib Monotherapy Exposure in Sponsor-Initiated Studies in Advanced RCC**

| Study number           | Description of trial                                                                              | Number of patients exposed* | Status     |
|------------------------|---------------------------------------------------------------------------------------------------|-----------------------------|------------|
| AV-951-15-303 (TIVO-3) | Phase 3 randomized trial, tivozanib vs. sorafenib, in relapsed/refractory patients                | 173                         | Ongoing    |
| AV-951-09-301 (TIVO-1) | Phase 3 randomized trial, tivozanib vs. sorafenib, in treatment-naïve patients                    | 259                         | Completed  |
| AV-951-09-902          | Phase 3 extension study of TIVO-1                                                                 | 161                         | Completed  |
| AV-951-10-202          | Phase 2 and biomarker study in treatment-naïve patients                                           | 105                         | Completed  |
| AV-951-12-205          | Phase 2 randomized patient preference study (tivozanib vs. sunitinib) in treatment-naïve patients | 38                          | Terminated |
| AV-951-07-201          | Phase 2 placebo-controlled discontinuation trial in treatment-naïve patients                      | 272                         | Completed  |

\*All patients were treated for advanced RCC and received tivozanib 1.34 mg daily for 21 days on treatment followed by 7 days off treatment for a 28-day cycle. Each patient listed in this table is unique; although AV-951-09-902 is an extension study of TIVO-1, the patients who received tivozanib in the extension study received sorafenib rather than tivozanib in TIVO-1.

Source: ADAE dataset (Integrated Summary of Safety)

Data from patients with non-RCC tumors or who received combination therapy are not included in the clinical safety portion of this review.

In TIVO-3, 175 patients were randomized to tivozanib, and 173 patients received at least 1 dose; 176 patients were randomized to sorafenib, and 170 patients received at least 1 dose. Thus, the clinical safety portion of this review will focus on the safety population from TIVO-3: n=173 for tivozanib and n=170 for sorafenib.

The median duration of exposure was longer in the tivozanib arm (197 days) than the sorafenib arm (140.5 days). The average number of cycles started (11.9 vs. 6.7) and median relative dose intensity (94.9 mg vs. 75.3 mg) were higher in the tivozanib arm compared with the sorafenib arm (Table B).

**Table 22. Study Drug Exposure in TIVO-3**

| Category/Statistic                            | Tivozanib<br>(n=173) | Sorafenib<br>(n=170) |
|-----------------------------------------------|----------------------|----------------------|
| Number of cycles started, mean                | 11.9                 | 6.7                  |
| <b>Duration of exposure, days<sup>1</sup></b> |                      |                      |
| Mean (std dev )                               | 335.8 (313.74)       | 191.9 (187.44)       |
| Min, max                                      | 4, 1124              | 7, 1099              |
| Median                                        | 197.0                | 145.0                |
| <b>Duration of exposure, months</b>           |                      |                      |
| < 1                                           | 5 (3%)               | 18 (11%)             |
| ≥ 1 and < 6                                   | 76 (44%)             | 90 (53%)             |
| ≥ 6                                           | 92 (53%)             | 62 (36%)             |
| <b>Relative dose intensity, %<sup>2</sup></b> |                      |                      |
| Mean (std dev )                               | 88.3 (15.3)          | 71.5 (25.2)          |
| Min, max                                      | 4.8, 105             | 8.8, 106.4           |
| Median                                        | 94.9                 | 75.3                 |

<sup>1</sup>Exposure = sum of the length of all the cycles.

Note: A cycle of tivozanib was considered to be 3 weeks of the study drug followed by 1 week of no study drug administration. A cycle of sorafenib was considered to be 4 weeks of the study drug.

<sup>2</sup>Relative Dose Intensity is defined as 100% times the Actual Dose Intensity (ADI) divided by the Intended Dose Intensity (IDI). ADI for a patient is defined as the total dose received over all cycles divided by the sum of the lengths of all cycles in days where the minimum cycle length is 28 days. IDI is the total dose assigned over all cycles divided by the sum of the intended lengths of all cycles in days.

**Reviewer Comment:** *The higher relative dose intensity reported for tivozanib indicates that fewer patients required dose reductions. This appears to support the conclusion that tivozanib's tolerability is within range for this patient population.*

**Relevant characteristics of the safety population:**

A total of 343 patients out of 350 randomized patients received at least 1 dose of study drug on the TIVO-3 study. Two patients randomized to tivozanib and 5 patients randomized to sorafenib did not receive treatment. Baseline demographic and disease characteristics for the full analysis set were generally well balanced between treatment arms as seen in Tables 8 and 9.

**Reviewer Comment:** *Most patients had an ECOG PS of 0 in both treatment arms, and we note*

*that it is unlikely that the general pool of patients in their third line of therapy would be expected to have this relatively high performance status.*

#### **Adequacy of the safety database:**

Overall exposure to tivozanib was adequate to support characterization of the safety profile in the proposed patient population.

### **8.2.3 Adequacy of Applicant's Clinical Safety Assessments**

#### **Issues Regarding Data Integrity and Submission Quality**

The NDA submission contained all required components of the eCTD. The overall quality and integrity of the application was adequate for substantive review to be completed. (b) (4)  
monitored sites for protocol adherence, completion and retention of eCRFs and source documentation. For a summary of FDA Clinical Inspection findings, refer to Section 4.1 of this review (Office of Scientific Investigation).

#### **Categorization of Adverse Events**

Adequate definitions for adverse events (AEs) were provided. All AEs were reported regardless of causality. AEs were coded using MedDRA Version 19.1 or later and graded using NCI CTCAE Version 4.03. TEAEs were defined as any AE with an onset date from the first dose of study treatment through 30 days after last dose of study treatment.

A safety overview of adverse events in TIVO-3 is shown in the table below.

**Table 23. Overview of Safety in TIVO-3**

|                                        | <b>Tivozanib<br/>(n=173)</b> | <b>Sorafenib<br/>(n=170)</b> |
|----------------------------------------|------------------------------|------------------------------|
| Grade 1-5 TEAEs, n (%)                 | 171 (99%)                    | 170 (100%)                   |
| Grade 3-4 TEAEs, n (%)                 | 115 (67%)                    | 123 (72%)                    |
| Serious TEAEs, n (%)                   | 78 (45%)                     | 67 (39%)                     |
| Deaths due to TEAEs within 30 days     | 12 (7.5%)                    | 9 (5.3%)                     |
| Treatment discontinuation due to TEAEs | 36 (21%)                     | 50 (29%)                     |
| Dose reduction due to TEAEs            | 41 (24%)                     | 65 (38%)                     |
| Dose interruption due to TEAEs         | 83 (48%)                     | 107 (63%)                    |

#### **Routine Clinical Tests**

The schedule of assessments for TIVO-3, as outlined in the protocol, is shown in the following table. The table depicts the frequency of laboratory testing, vital signs, physical exam, and adverse event monitoring.

**Table 24. Schedule of Safety Assessments**

| STUDY PROCEDURES                        | SCREEN         | CYCLE 1                                                                                       |                          | CYCLE 2                           | SUBSEQUENT CYCLES                 | END OF TREATMENT (up to 7 days after last dose) <sup>f</sup> | 30-DAY FOLLOW-UP (±7 days) | UNSCHEDED <sup>g</sup> | LONG TERM RESPONSE & SURVIVAL FOLLOW-UP |                |
|-----------------------------------------|----------------|-----------------------------------------------------------------------------------------------|--------------------------|-----------------------------------|-----------------------------------|--------------------------------------------------------------|----------------------------|------------------------|-----------------------------------------|----------------|
|                                         |                | 1                                                                                             | 15 ± 2 days <sup>p</sup> | 1 ± 2 days <sup>p</sup>           | 1 ± 2 days <sup>p</sup>           |                                                              |                            |                        |                                         |                |
| Cycle Day                               | -21 to -1      | 1                                                                                             | 15 ± 2 days <sup>p</sup> | 1 ± 2 days <sup>p</sup>           | 1 ± 2 days <sup>p</sup>           |                                                              |                            |                        |                                         |                |
| Concomitant Medications                 | X              | Collected from the date informed consent form signed to 30 days after last dose of study drug |                          |                                   |                                   |                                                              |                            |                        |                                         |                |
| Adverse Event                           | X              | Collected from the date informed consent form signed to 30 days after last dose of study drug |                          |                                   |                                   |                                                              |                            |                        |                                         |                |
| Study Drug Administration               |                | Daily x 3 or 4 weeks <sup>q</sup>                                                             |                          | Daily x 3 or 4 weeks <sup>q</sup> | Daily x 3 or 4 weeks <sup>q</sup> |                                                              |                            |                        |                                         |                |
| ECOG Performance Status                 | X              | X <sup>i</sup>                                                                                | X                        | X                                 | X                                 | X                                                            | X                          | X                      |                                         |                |
| Vital Signs                             | X              | X                                                                                             | X                        | X                                 | X                                 | X                                                            | X                          | X                      |                                         |                |
| Physical Examination <sup>b</sup>       | X              | X <sup>i</sup>                                                                                | X                        | X                                 | X                                 | X                                                            | X                          | X                      |                                         |                |
| Hematology <sup>c</sup>                 | X              | X <sup>i</sup>                                                                                | X                        | X                                 | X                                 | X                                                            | X                          | X                      |                                         |                |
| Serum Chemistries <sup>d</sup>          | X              | X <sup>i</sup>                                                                                | X                        | X                                 | X                                 | X                                                            | X                          | X                      |                                         |                |
| Coagulation Parameters <sup>e</sup>     | X              | X <sup>i</sup>                                                                                | X                        | X                                 | X                                 | X                                                            | X                          | X                      |                                         |                |
| Thyroid Function Tests <sup>f</sup>     | X              |                                                                                               |                          | X                                 | X <sup>g</sup>                    | X                                                            | X                          | X                      |                                         |                |
| Urinalysis <sup>h</sup>                 | X              | X <sup>i</sup>                                                                                | X                        | X                                 | X                                 | X                                                            | X                          | X                      |                                         |                |
| Pregnancy Test <sup>i</sup>             | X              |                                                                                               |                          |                                   |                                   | X                                                            |                            | X                      |                                         |                |
| 12-Lead ECG                             | X              |                                                                                               |                          |                                   |                                   | X                                                            | X                          | X                      |                                         |                |
| Disease / Response Assessment (CT/MRI)  | X <sup>k</sup> | Every 8 weeks (±3 days) from Cycle 1, Day 1                                                   |                          |                                   |                                   |                                                              | X <sup>l</sup>             |                        | X                                       | X <sup>m</sup> |
| Study Drug Diary                        |                | X                                                                                             | X                        | X                                 | X                                 | X                                                            |                            | X                      |                                         |                |
| Pharmacokinetics <sup>n</sup>           |                | X                                                                                             | X                        |                                   |                                   |                                                              |                            |                        |                                         |                |
| Contact of patient by site <sup>o</sup> |                |                                                                                               |                          |                                   |                                   |                                                              |                            |                        | X                                       |                |

a Physical exams (PE) included height (at Screening visit only) and weight; directed PE thereafter, including weight.

b Hematology included complete blood count (CBC) with differential and platelet count.

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- c Serum chemistries included sodium, potassium, chloride, bicarbonate (optional), blood urea nitrogen (BUN), creatinine, glucose, total bilirubin, direct bilirubin, AST, ALT, lactate dehydrogenase (LDH), alkaline phosphatase, calcium, magnesium, phosphorous, albumin, amylase, lipase, and total protein.
- d Coagulation parameters included prothrombin time (PT) and/or international normalized ratio (INR), and partial thromboplastin time (PTT).
- e Total T3 (triiodothyronine) (optional), free T4 (thyroxine), and thyroid stimulating hormone (TSH) levels.
- f Performed during every even-numbered cycle beyond Cycle 2 (i.e., Cycle 4, 6, 8 etc.).
- g Urinalysis included protein, glucose, ketones, urobilinogen, occult blood, and microscopic sediment evaluation. A 24-hour urine for protein collected whenever protein was 4+.
- h Prior to Cycle 1: Performed prior to first dose; not assessed again if  $\leq 7$  days since corresponding assessment performed at screening.
- i Pregnancy test: Serum  $\beta$ -hCG required for premenopausal, non-sterilized females.
- j Screening CT/MRI scan performed up to 30 days prior to first dose as part of standard of care, and prior to signing of the informed consent if performed in compliance with the protocol requirements. Screening scan included head, chest, abdomen, and pelvis.
- k Not needed if last scan was within 30 days prior to End-of-Treatment (EOT) Visit and showed progressive disease (PD), as confirmed by independent radiology review. Starting with version 5 of the protocol, all clinical response decisions were based on local radiological review.
- l For patients with stable disease or objective response at the time of treatment discontinuation, who discontinued for reasons other than radiological evidence of progressive disease, tumor assessments continued to be collected (every 2 months during the first year [beginning from the date of the last scan performed prior to treatment discontinuation], every 3 months during the second year, and every 6 months thereafter) until disease progression confirmed by independent radiology review or start of another therapy. A  $\pm 3$  day visit window applied to tumor assessments for patients who discontinued study drug. Starting with version 5 of the protocol, all clinical response decisions were based on local radiological review.
- m Two blood samples for pharmacokinetic (PK) analysis were collected at the following time points from all patients: Cycle 1, Day 1-4 hours post-dose and Cycle 1, Day 15- pre-dose (within 2 hours before dosing).
- n After the 30-Day Follow-up visit, patients were contacted once every 3 months by the site to collect long-term survival data. Additional contacts may have been made to support key analyses, such as the analysis of overall survival at the time of the final PFS analysis, and the final analysis of overall survival. A  $\pm 7$  day window applied for the scheduled long term follow-up contacts.
- o A  $\pm 2$  day window applied to all visit procedures except study drug administration.
- p The duration of treatment for tivozanib is 21 of 28 days, and for sorafenib is 28 of 28 days.
- q All patients had an EOT visit when they permanently discontinued any further study treatment. The EOT visit occurred up to 7 days after the last dose of study drug. Assessments performed within 3 days of the EOT visit did not need to be repeated and may have been documented as the EOT assessment (except for the response assessment which did not need to be repeated if performed within 30 days and showed progressive disease). Patients starting new anti-cancer therapy after the last dose of study drug completed the EOT Visit assessments in advance of starting the new anti-cancer therapy.
- r Assessments obtained/ performed/ measured as clinically indicated.

## 8.2.4 Safety Results

### Deaths

All deaths on the TIVO-3 study are summarized in the table below. A total of 29 deaths occurred within 30 days of last study treatment and 21 of these deaths were associated with an AE: 12 patients (7.5%) in the tivozanib arm and 9 patients (5.3%) in the sorafenib arm.

**Table 25. Deaths on TIVO-3**

|                                            | <b>Tivozanib<br/>(n=173)</b> | <b>Sorafenib<br/>(n=170)</b> |
|--------------------------------------------|------------------------------|------------------------------|
| Deaths on study treatment, n (%)           | 16 (9.3%)                    | 13 (7.6%)                    |
| Deaths due to progressive disease, n (%)   | 4 (2.3%)                     | 5 (2.9%)                     |
| Deaths due to an adverse event, n (%)      | 12 (7.5%)                    | 9 (5.3%)                     |
| Pneumonia                                  | 3                            | 2                            |
| Respiratory failure/arrest                 | 2                            | 2                            |
| Death/multiple organ dysfunction syndrome* | 2                            | 2                            |
| Hepatic failure/hepatobiliary disease      | 2                            | 0                            |
| Cardio-respiratory arrest                  | 1                            | 0                            |
| Subdural hematoma                          | 1                            | 0                            |
| Cerebrovascular accident                   | 1                            | 0                            |
| Cachexia                                   | 0                            | 1                            |
| Cardiac failure                            | 0                            | 1                            |
| Coma                                       | 0                            | 1                            |

Source: ADAE (USUBJID, TRT01A, TRTEMFL, AETOXGR). Data cutoff: May 1, 2020.

\*These are grouped together because the narratives contained little information and the reviewer's assessment is that the cause of death is unclear.

Narratives for the TEAEs, excluding "neoplasm progression," leading to death are provided below. None of the AEs leading to death were considered "related" to tivozanib by the investigator. Of the 12 TEAEs leading to death, half (6/12) occurred concurrently with documented disease progression which may have contributed to death.

According to this reviewer's assessment, 4 of the remaining 6 cases may have been related to tivozanib. Patient (b) (6) pneumonia is unlikely to be related to the drug because 1-2 doses of a drug that is dosed daily continuously is typically not adequate exposure to cause an infection. Patient (b) (6) multiple organ dysfunction syndrome is also unlikely to be related to the drug because the direct cause of death was that he stopped drinking and eating, which occurred a few weeks after stopping tivozanib. Therefore, the 4 remaining patients whose deaths were due to an AE which did not occur in the context of disease progression may have been related to the study drug, as the narratives did not provide information to suggest otherwise.

| <b>Patient (SUBJID);<br/>Preferred Term</b> | <b>Possibly<br/>related<br/>(per<br/>reviewer)</b> | <b>Narrative</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
|---------------------------------------------|----------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| (b) (6)<br><u>subdural<br/>hematoma</u>     |                                                    | 69-year-old man with PMH of aortic valve replacement: on day 90, the patient had symptoms of stroke. MRI was suggestive of possible embolic event. Started therapeutic enoxaparin. Approximately 3 weeks later, tivozanib was permanently discontinued due to PD. Two weeks after the last dose, he fell and had subdural hematoma.                                                                                                                                                                                                               |
| (b) (6)<br><u>pneumonia</u>                 |                                                    | 59-year-old woman with metastases to bones and liver, prior treatment with sunitinib, axitinib, and nivolumab, was hospitalized for pneumonia on study day 2.                                                                                                                                                                                                                                                                                                                                                                                     |
| (b) (6)<br><u>respiratory failure</u>       | Yes                                                | 79-year-old man with metastases to lung had cachexia/general deterioration for the first 1.5 months on study leading to tivozanib discontinuation on day 46. Twelve days later, the patient died but there was no explanation of the cause of respiratory failure.                                                                                                                                                                                                                                                                                |
| (b) (6);<br><u>hepatic failure</u>          |                                                    | 51-year-old woman with metastases to bones and liver and PMH of a “liver disorder since 1990” was found to have hyperammonemia with confusional state on day 132. She was treated in the hospital for 9 days but re-admitted for the same reason on day 153. She died day 169 due to hepatic failure, related to disease progression and underlying unspecified liver condition.                                                                                                                                                                  |
| (b) (6)<br><u>death</u>                     | Yes                                                | 74-year-old man with metastases to bone and liver, PMH of COPD since 2007; hypertrophic cardiomyopathy, HTN, and TIA 2016, had stable disease on tivozanib for the first 4 months (through day 127). Day 101: grade 3 COPD and CHF exacerbation, grade 3 HTN. Discharged 12 days later. Day 142, he died without any anticipatory symptom.                                                                                                                                                                                                        |
| (b) (6)<br><u>pneumonia</u>                 |                                                    | 60-year-old woman with metastases to liver and lungs and PMH of DM, HTN, and hypothyroidism, had stable disease for the first 4 months (through day 114). On day 143, she had grade 2 dyspnea and fever, which led to discontinuation of tivozanib. Symptoms worsened with discontinuation. She died 3 weeks later.<br><br><i>Reviewer’s assessment: since the patient had disease in lung and she worsened with discontinuation, the narrative suggests her symptoms were due to progression which may not have been shown radiographically.</i> |

|                                                                |            |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
|----------------------------------------------------------------|------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <p>(b) (6)<br/> <u>pneumonia</u></p>                           | <p>Yes</p> | <p>61-year-old man with left temporal lobectomy and RT to brain and intrabronchial RT to lung had stable disease on tivozanib for the first 4 months (through day 114). Day 164: ischemic stroke which led to pneumonia 3 days later. He died 2 days later from respiratory failure and pneumonia. <i>Reviewer's assessment: Each patient should have only one grade 5 AE. Therefore, this reviewer only counts pneumonia, because it is a more specific term and to avoid counting patients twice, when summarizing grade 5 AEs.</i></p>         |
| <p>(b) (6)<br/> <u>cerebrovascular accident</u></p>            |            | <p>62-year-old man without history of hypertension or other risk factors had well-controlled blood pressure throughout the first 5 months of tivozanib. He had progression of disease on day 113 and discontinued therapy on day 159. Day 162: CVA. Died 2 weeks later.<br/> <i>Reviewer's assessment: The narrative does not contain adequate information to discern the cause of CVA, but PD with hypercoagulability due to cancer is a potential cause.</i></p>                                                                                |
| <p>(b) (6)<br/> <u>multiple organ dysfunction syndrome</u></p> |            | <p>51-year-old man with metastases to liver and pancreas was hospitalized on day 29 for hyperbilirubinemia (direct bilirubin 4.4 mg/dL), bone pain, vomiting, severe depression. Permanent discontinuation of study drug that day. He stopped drinking, eating, and taking medications a few weeks later which led to death on day 50.<br/> <i>Reviewer's assessment: The narrative is unclear but it appears that the patient may have been depressed, which may have been partly due to disease progression, which led to malnutrition.</i></p> |
| <p>(b) (6)<br/> <u>cardiopulmonary arrest</u></p>              |            | <p>66-year-old man with history of CHF, COPD, and HTN was taking amiodarone, furosemide, enoxaparin for prophylaxis cardiac comorbidities. On day 74, he was hospitalized for lung infection due to PD. COPD exacerbation and delirium resulted. Tivozanib was interrupted; 20 days after last dose, he had cardio-respiratory arrest due to lung infection</p>                                                                                                                                                                                   |
| <p>(b) (6)<br/> <u>hepatobiliary disease</u></p>               |            | <p>68-year-old man with metastases to liver had scans demonstrating PD (per both investigator and independent review) after 10 months of tivozanib. Tivozanib discontinued on day 310. Day 330: U/S showed stone in duct. Direct bili was 235 U/L (13.7mg/dL). Patient died the next day. Autopsy performed but results not provided.<br/> <i>Reviewer's assessment: The sequence of events suggests that progression of liver metastases was the cause of death, because scans unequivocally showed PD 6 weeks prior to</i></p>                  |

|                                             |     |                                                                                                                                                                                                                                                                                                                                                                                      |
|---------------------------------------------|-----|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                             |     | <i>death. This is unlikely to be caused by tivozanib since it had been discontinued 20 days before the event.</i>                                                                                                                                                                                                                                                                    |
| (b) (6)<br><u>acute respiratory failure</u> | Yes | 61-year-old man with history of radiation to lung and emphysema. Had stable disease (first and only radiographic assessment, day 57) on tivozanib. Continued to take tivozanib up through the day of death (day 99) when he died of acute respiratory failure. No information surrounding the event provided. Per PCP, the respiratory failure was due to patient's chronic smoking. |

**Reviewer comment:** As noted in Table 25, the Grade 5 adverse event Preferred Term was “Neoplasm progression.” After review of the narratives, this reviewer agrees that the 4 deaths were due to progressive disease. These are not included in the table above or in the label for the purpose of consistency with other patients who died due to disease progression. These other patients (n=59) were coded as having DTHREA (reason for death) in the ADSL dataset of “DISEASE UNDER STUDY” and would not have any Grade 5 adverse events in the ADAE dataset. As noted in Table 24, the Grade 5 adverse event Preferred Term was “Neoplasm progression.” After review of the narratives, this reviewer agrees that the 4 deaths were due to progressive disease. These are not included in the table above or in the label for the purpose of consistency with other patients who died due to disease progression. These other patients (n=59) were coded as having DTHREA (reason for death) in the ADSL dataset of “DISEASE UNDER STUDY” and would not have any Grade 5 adverse events in the ADAE dataset.

### Serious Adverse Events

Table F. SAEs that occurred in >2 patients in either treatment arm of TIVO-3

| Treatment-emergent adverse event <sup>1</sup> , n (%) | Tivozanib<br>(n=173) | Sorafenib<br>(n=170) |
|-------------------------------------------------------|----------------------|----------------------|
| Any SAE                                               | 78 (45%)             | 67 (39%)             |
| Bleeding <sup>2</sup>                                 | 6 (3.5%)             | 3 (1.8%)             |
| Venous thromboembolism <sup>3</sup>                   | 6 (3.5%)             | 0 (0%)               |
| Arterial thromboembolism <sup>4</sup>                 | 5 (2.9%)             | 9 (5.3%)             |
| Pneumonia (PT)                                        | 5 (2.9%)             | 5 (2.9%)             |
| Acute kidney injury <sup>5</sup>                      | 4 (2.3%)             | 3 (1.8%)             |
| Hepatobiliary disorders <sup>6</sup>                  | 4 (2.3%)             | 0 (0%)               |
| Fatigue <sup>7</sup>                                  | 3 (1.7%)             | 2 (1.2%)             |
| Confusional state (PT)                                | 3 (1.7%)             | 0 (0%)               |
| Decreased appetite (PT)                               | 3 (1.7%)             | 1 (0.6%)             |
| Pleural effusion (PT)                                 | 3 (1.7%)             | 1 (0.6%)             |
| Urinary tract infection (PT)                          | 3 (1.7%)             | 1 (0.6%)             |
| Vomiting (PT)                                         | 1 (0.6%)             | 3 (1.8%)             |

Source: ADAE (USUBJID, TRT01A, TRTEMFL, AESER, AETOXGR). Data cutoff: May 1, 2020.

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Abbreviations: PT, Preferred Term; SAE, Serious Adverse Event

<sup>1</sup>Excluding “neoplasm progression” and “death” as PTs

<sup>2</sup>Includes gastrointestinal haemorrhage, haematuria, haemoptysis, melaena, rectal haemorrhage, subdural haematoma

<sup>3</sup>Includes pulmonary embolism and deep vein thrombosis. Includes ischaemic stroke, acute coronary syndrome, myocardial infarction, transient ischaemic attack

<sup>4</sup>Includes ischaemic stroke, acute coronary syndrome, myocardial infarction, transient ischaemic attack

<sup>5</sup>Includes acute kidney injury, renal failure, blood creatinine increased

<sup>6</sup>Includes hepatic failure, hepatobiliary disease, hyperbilirubinaemia, jaundice

<sup>7</sup>Includes fatigue, asthenia

**Reviewer Comment:** The overall incidence of SAEs was similar in the two treatment arms (Table F). The most common SAEs in either treatment arm were consistent with the known safety profile of kinase inhibitors.

### Dropouts and/or Discontinuations Due to Adverse Effects

Discontinuations due to TEAE on the TIVO-3 study are summarized in the table below. Permanent discontinuation of study drug due to TEAE occurred in 21% of patients of the tivozanib safety population and 29% of the sorafenib safety population. TEAEs which resulted in permanent discontinuation of FOTIVDA in > 2 patients included hepatobiliary disorders, fatigue, and pneumonia.

Table 26. Discontinuations Due to TEAE in >1 Patient in Either Arm on TIVO-3

|                                                   | <b>Tivozanib<br/>(n=173)</b> | <b>Sorafenib<br/>(n=170)</b> |
|---------------------------------------------------|------------------------------|------------------------------|
| Discontinuations due to TEAE <sup>1</sup> , n (%) | 36 (21%)                     | 50 (29%)                     |
| Hepatobiliary disorders <sup>2</sup>              | 5 (2.9%)                     | 1 (0.6%)                     |
| Fatigue <sup>3</sup>                              | 3 (1.7%)                     | 8 (4.7%)                     |
| Pneumonia (PT)                                    | 3 (1.7%)                     | 3 (1.8%)                     |
| Vomiting (PT)                                     | 2 (1.2%)                     | 1 (0.6%)                     |
| Cerebrovascular accident (PT)                     | 2 (1.2%)                     | 1 (0.6%)                     |
| Hypothyroidism (PT)                               | 2 (1.2%)                     | 0                            |
| Rash <sup>4</sup>                                 | 0                            | 8 (4.7%)                     |
| Diarrhea (PT)                                     | 1                            | 4 (2.4%)                     |
| Palmar-plantar erythrodysesthesia (PT)            | 0                            | 3 (1.8%)                     |
| Acute kidney injury <sup>5</sup>                  | 1                            | 2 (1.2%)                     |
| Arterial thromboembolism <sup>6</sup>             | 1                            | 2 (1.2%)                     |
| Dyspnea (PT)                                      | 1                            | 2 (1.2%)                     |
| Bleeding <sup>7</sup>                             | 0                            | 2 (1.2%)                     |

Source: ADAE (USUBJID, TRT01A, TRTEMFL, AEDISCON). Data cutoff: August 15, 2019.

Abbreviations: PT, Preferred Term

<sup>1</sup>Excluding “neoplasm progression”.

<sup>2</sup>Includes hepatic failure, blood alkaline phosphatase increased, blood bilirubin increased, hepatobiliary disease, hyperbilirubinaemia, jaundice

<sup>3</sup>Includes fatigue and asthenia

<sup>4</sup>Includes rash, rash maculo-papular, rash generalised

<sup>5</sup>Includes acute kidney injury, renal failure, renal impairment

<sup>6</sup>Includes acute coronary syndrome and myocardial infarction

<sup>7</sup>Includes hemoptysis and hemorrhage intracranial

**Reviewer Comment:** Fatigue was a common TEAE overall, but most patients experienced low-grade fatigue which did not require treatment discontinuation (Table G). The finding that a higher proportion of patients in the sorafenib arm required discontinuation for fatigue is consistent with the PROs.

Table 27. Dose Interruptions Due to TEAE in >5% of Patients in Either Arm on TIVO-3

|                                        | <b>Tivozanib<br/>(n=173)</b> | <b>Sorafenib<br/>(n=170)</b> |
|----------------------------------------|------------------------------|------------------------------|
| Dose interruptions due to TEAE, n (%)  | 83 (48%)                     | 107 (63%)                    |
| Fatigue <sup>1</sup>                   | 18 (10.4%)                   | 23 (13.5%)                   |
| Hypertension (PT)                      | 13 (7.5%)                    | 10 (5.9%)                    |
| Decreased appetite (PT)                | 9 (5.2%)                     | 12 (7.1%)                    |
| Nausea (PT)                            | 9 (5.2%)                     | 18 (10.6%)                   |
| Rash <sup>2</sup>                      | 4 (2.3%)                     | 31 (18.2%)                   |
| Palmar-plantar erythrodysesthesia (PT) | 4 (2.3%)                     | 29 (17.1%)                   |
| Diarrhea (PT)                          | 7 (4%)                       | 19 (11.2%)                   |

Source: ADAE (USUBJID, TRT01A, TRTEMFL, AEDOSINT). Data cutoff: August 15, 2019.

Abbreviations: PT, Preferred Term

<sup>1</sup>Includes fatigue and asthenia

<sup>2</sup>Includes rash, rash maculo-papular, rash generalised

Table 28. Dose Reductions Due to TEAE in >3% of Patients in Either Arm on TIVO-3

|                                        | <b>Tivozanib<br/>(n=173)</b> | <b>Sorafenib<br/>(n=170)</b> |
|----------------------------------------|------------------------------|------------------------------|
| Dose reductions due to TEAE, n (%)     | 41 (24%)                     | 65 (38%)                     |
| Fatigue <sup>1</sup>                   | 12 (6.9%)                    | 12 (7.1%)                    |
| Diarrhea (PT)                          | 6 (3.5%)                     | 15 (8.8%)                    |
| Decreased appetite (PT)                | 6 (3.5%)                     | 6 (3.5%)                     |
| Palmar-plantar erythrodysesthesia (PT) | 1 (0.6%)                     | 19 (11.2%)                   |
| Rash <sup>2</sup>                      | 2 (1.2%)                     | 15 (8.8%)                    |

Source: ADAE (USUBJID, TRT01A, TRTEMFL, AEDOSINT). Data cutoff: August 15, 2019.

Abbreviations: PT, Preferred Term

<sup>1</sup>Includes fatigue and asthenia

<sup>2</sup>Includes erythema, rash, rash maculo-papular

## Significant Adverse Events

Adverse events of interest (...) are described in section 8.2.5, Analysis of Submission-Specific Safety Issues. Grade 3-5 TEAEs occurred in 73% vs. 81% in the tivozanib and sorafenib

arms, respectively, in TIVO-3. Grade 3-4 TEAEs occurred in 64% vs. 73% in the tivozanib and sorafenib arms, respectively, in TIVO-3 and are described below in the Treatment Emergent Adverse Events and Adverse Reactions section.

### Treatment Emergent Adverse Events and Adverse Reactions

Table 29. TEAEs That Occurred in >10% of Patients in Either Treatment Arm on TIVO-3

|                                        | Tivozanib<br>(n=173) |              | Sorafenib<br>(n=170) |              |
|----------------------------------------|----------------------|--------------|----------------------|--------------|
|                                        | All Grades           | Grade 3 or 4 | All Grades           | Grade 3 or 4 |
| Any TEAE, n (%)                        | 171 (99%)            | 115 (67%)    | 170 (100%)           | 123 (72%)    |
| General                                |                      |              |                      |              |
| Fatigue <sup>1</sup>                   | 115 (67%)            | 22 (13%)     | 81 (48%)             | 21 (12%)     |
| Edema <sup>2</sup>                     | 18 (10%)             | 0            | 18 (11%)             | 0            |
| Vascular                               |                      |              |                      |              |
| Hypertension <sup>3</sup>              | 76 (44%)             | 42 (24%)     | 52 (31%)             | 28 (17%)     |
| Bleeding <sup>4</sup>                  | 30 (17%)             | 5 (2.9%)     | 21 (12%)             | 2 (1.2%)     |
| Gastrointestinal                       |                      |              |                      |              |
| Diarrhea <sup>5</sup>                  | 74 (43%)             | 3 (1.7%)     | 91 (54%)             | 19 (11.2%)   |
| Nausea (PT)                            | 51 (30%)             | 0            | 31 (18%)             | 6 (3.5%)     |
| Stomatitis (PT)                        | 36 (21%)             | 3 (1.7%)     | 39 (23%)             | 4 (2.4%)     |
| Vomiting (PT)                          | 31 (18%)             | 2 (1.2%)     | 28 (17%)             | 4 (2.4%)     |
| Abdominal pain (PT)                    | 20 (12%)             | 3 (1.7%)     | 18 (11%)             | 4 (2.4%)     |
| Constipation (PT)                      | 18 (10%)             | 0            | 24 (14%)             | 1 (0.6%)     |
| Metabolism and nutrition               |                      |              |                      |              |
| Decreased appetite (PT)                | 67 (39%)             | 8 (4.6%)     | 51 (30%)             | 6 (3.5%)     |
| Respiratory, thoracic, and mediastinal |                      |              |                      |              |
| Dysphonia (PT)                         | 47 (27%)             | 1 (0.6%)     | 16 (9.4%)            | 0            |
| Cough (PT)                             | 38 (22%)             | 0            | 26 (15.3%)           | 1 (0.6%)     |
| Dyspnea (PT)                           | 26 (15%)             | 5 (2.9%)     | 18 (10.6%)           | 2 (1.2%)     |
| Endocrine                              |                      |              |                      |              |
| Hypothyroidism <sup>6</sup>            | 41 (24%)             | 1 (0.6%)     | 18 (10.6%)           | 0            |
| Musculoskeletal                        |                      |              |                      |              |
| Back pain (PT)                         | 32 (19%)             | 3 (1.7%)     | 27 (16%)             | 4 (2.4%)     |
| Skin and subcutaneous tissue disorders |                      |              |                      |              |
| Rash <sup>7</sup>                      | 31 (18%)             | 2 (1.2%)     | 88 (52%)             | 26 (15%)     |
| Palmar-plantar erythrodysesthesia (PT) | 28 (16%)             | 2 (1.2%)     | 69 (41%)             | 17 (10%)     |
| Investigations                         |                      |              |                      |              |
| Weight decreased (PT)                  | 29 (17%)             | 5 (2.9%)     | 37 (22%)             | 5 (2.9%)     |
| Nervous system disorders               |                      |              |                      |              |
| Headache (PT)                          | 20 (12%)             | 3 (1.7%)     | 16 (9.4%)            | 0            |

Source: ADAE (USUBJID, TRT01A, TRTEMFL, AETOXGR). Data cutoff: May 1, 2020.

Abbreviations: PT, Preferred Term

<sup>1</sup>Includes fatigue and asthenia

<sup>2</sup>Includes edema, edema peripheral, and localized edema

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<sup>3</sup>Includes hypertension, blood pressure increased, hypertensive crisis

<sup>4</sup>Includes hematuria, epistaxis, hemoptysis, hematoma, rectal hemorrhage, vaginal hemorrhage, contusion, gastrointestinal hemorrhage, hematochezia, intraocular hematoma, melena, metrorrhagia, pulmonary hemorrhage, subdural hematoma, gingival bleeding, hematemesis, hemorrhage intracranial, hemorrhoidal hemorrhage, splinter hemorrhages

<sup>5</sup>Includes diarrhea and frequent bowel movements

<sup>6</sup>Includes hypothyroidism, blood thyroid stimulating hormone increased, tri-iodothyronine decreased, tri-iodothyronine free decreased

<sup>7</sup>Includes dermatitis, dermatitis acneiform, dermatitis contact, drug eruption, eczema, eczema nummular, erythema, erythema multiforme, photosensitivity reaction, pruritus, psoriasis, rash, rash erythematous, rash generalized, rash macular, rash maculopapular, rash morbilliform, rash pruritic, seborrheic dermatitis, skin exfoliation, skin irritation, skin lesion, swelling face, toxic skin eruption, urticaria

**Reviewer Comment:** TEAEs that differ by >5% between the two arms and that are higher in the tivozanib treatment arm include: fatigue, hypertension, nausea, decreased appetite, dysphonia, cough, and hypothyroidism. TEAEs that differ by >5% between the two arms and that are higher in the sorafenib arm include: diarrhea and palmar-plantar erythrodysesthesia syndrome.

## Laboratory Findings

Table 30. Laboratory Abnormalities (≥ 10%) That Worsened from Baseline in Either Treatment Arm on TIVO-3

|                                | Tivozanib<br>(n=173) |              | Sorafenib<br>(n=170) |              |
|--------------------------------|----------------------|--------------|----------------------|--------------|
|                                | All Grades           | Grade 3 or 4 | All Grades           | Grade 3 or 4 |
| <b>Hematology</b>              |                      |              |                      |              |
| Lymphocytes decreased          | 37 (25%)             | 7 (4.7%)     | 59 (42%)             | 8 (5.8%)     |
| Hemoglobin increased           | 33 (19%)             | 0            | 14 (8%)              | 0            |
| Platelets decreased            | 33 (19%)             | 0            | 30 (18%)             | 2 (1.2%)     |
| Hemoglobin decreased           | 27 (16%)             | 2 (1.2%)     | 46 (27%)             | 6 (3.6%)     |
| <b>Chemistry</b>               |                      |              |                      |              |
| Creatinine increased           | 86 (50%)             | 0            | 62 (37%)             | 1 (0.6%)     |
| Glucose increased              | 85 (50%)             | 5 (2.9%)     | 66 (40%)             | 0            |
| Albumin decreased              | 71 (42%)             | 3 (1.7%)     | 56 (34%)             | 4 (2.4%)     |
| Phosphate decreased            | 62 (38%)             | 9 (5%)       | 111 (66%)            | 51 (31%)     |
| Sodium decreased               | 62 (36%)             | 16 (9.4%)    | 51 (30%)             | 19 (11%)     |
| Lipase increased               | 51 (32%)             | 14 (8.7%)    | 55 (36%)             | 16 (10%)     |
| ALT increased                  | 52 (30%)             | 6 (3.6%)     | 48 (29%)             | 4 (2.4%)     |
| Alkaline phosphatase increased | 51 (30%)             | 6 (3.6%)     | 52 (31%)             | 3 (1.8%)     |
| AST increased                  | 47 (28%)             | 2 (1.2%)     | 52 (31%)             | 3 (1.8%)     |
| Potassium increased            | 15 (8.8%)            | 0            | 26 (16%)             | 0            |
| Magnesium decreased            | 44 (26%)             | 0            | 37 (23%)             | 2 (1.2%)     |
| Amylase increased              | 37 (23%)             | 3 (1.8%)     | 44 (28%)             | 4 (2.6%)     |
| Calcium increased              | 26 (15%)             | 3 (1.8%)     | 11 (6.5%)            | 3 (1.8%)     |

|                                                 | Tivozanib<br>(n=173) |          | Sorafenib<br>(n=170) |   |
|-------------------------------------------------|----------------------|----------|----------------------|---|
| Bilirubin increased                             | 19 (11%)             | 5 (3.0%) | 18 (11%)             | 0 |
| Coagulation                                     |                      |          |                      |   |
| Activated partial thromboplastin time prolonged | 41 (26%)             | 1 (0.6%) | 28 (18%)             | 0 |

Source: ADLB (USUBJID, TRT01A, PARAM, AVAL, PARAMLO, PARAMHI, AGRADE). Data cutoff: August 15, 2019.

The denominator used to calculate the rate varied from 139 to 171 based on the number of patients with a baseline value and at least one post-treatment value. Thus, percentages among lab abnormalities may be the same while the number of patients with that lab abnormality are different (e.g., for phosphate, 165 patients were evaluable, so n=62 is 38% of the tivo arm, while for sodium, 171 patients were evaluable, so n=62 is 36% of the tivo arm).

**Reviewer comment:** Laboratory abnormalities that differ by >5% and that were higher in the tivozanib arm include: hemoglobin increased, creatinine increased, glucose increased, albumin decreased, sodium decreased, calcium increased, and activated partial thromboplastin time prolonged. However, for each of these laboratory parameters, the difference between the tivozanib and sorafenib arm incidence of grade 3-4 events was less than 3%, with some of them being higher in the sorafenib arm, suggesting that most of these differences between arms are not clinically meaningful.

Both low and high hemoglobin were common. The upper quartile for hemoglobin values among all patients in TIVO-3 ranged from 15.6 to 21.2 mg/dL. The lower quartile ranged from 8.3 mg/dL to 13 mg/dL. Increased hemoglobin has been noted in association with VEGF inhibitors, which may be due to stimulation of erythropoietin production (<https://ashpublications.org/blood/article/112/11/3453/59882/Increased-Hemoglobin-Associated-with-VEGF>).

## Vital Signs

Systolic blood pressure changes from baseline ranged from -14.0 mmHg to 8.2 mmHg (tivozanib arm) and -9.7 mmHg to 6.6 mmHg (sorafenib arm). Diastolic blood pressure changes from baseline ranged from -0.7 mmHg to 7.4 mmHg (tivozanib arm) and -3.0 mmHg to 7.0 mmHg (sorafenib arm).

Abnormally high systolic blood pressure values ( $\geq 180$  mmHg) were observed in 1.4% of patients in the tivozanib arm and 5.3% in the sorafenib arm (Table 14.3.4.13). Abnormally low systolic blood pressure ( $\leq 80$  mmHg) was observed in 1.2% of patients in the tivozanib arm and 1.0% of patients in the sorafenib arm.

Abnormally high diastolic blood pressure values ( $\geq 105$  mmHg) were observed in 6.3% of patients in the tivozanib arm and 8.0% of patients in the sorafenib arm. Abnormally low diastolic blood pressure ( $\leq 50$  mmHg) was observed in 5.6% (tivozanib arm) and 2.3% (sorafenib arm) of patients.

Other than the effects on blood pressure, no clinically relevant trends in vital signs were evident during the study. See Section 8.2.5.1 for description and assessment of hypertension AEs.

### Electrocardiograms (ECGs)

The ECG data showed no evidence of any clinically meaningful effect of treatment on heart rate or ECG morphology.

### QT

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 (tivozanib hydrochloride) once daily for 21 days, which covers the therapeutic exposures of tivozanib. The data were analyzed using the exposure-response analysis as the primary analysis.

No large (>20 msec) QTc prolongation effect of tivozanib was detected. However, FDA is 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).

### Immunogenicity

Not applicable.

## 8.2.5 Analysis of Submission-Specific Safety Issues

Discussion of the Submission-Specific Safety Issues will focus on the Warnings and Precautions of labeling. Issues are presented in the order listed in Section 5 of labeling, followed by other AEs of interest. All AEs listed in the section below are reported in other labeling for drugs targeting the VEGF pathway.

### 8.2.5.1 Hypertension and Hypertensive Crisis

Hypertension was the most common grade 3-4 event in TIVO-3 in either treatment arm. In both TIVO-1 and TIVO-3, patients in the tivozanib arm had a higher incidence of hypertension compared to patients in the sorafenib arm. This was true for all-grade events as well as grade 3-4 events.

Table . Hypertension in Tivozanib vs. Sorafenib in TIVO-3 and TIVO-1

|                           | TIVO-3               |                      | TIVO-1               |                      |
|---------------------------|----------------------|----------------------|----------------------|----------------------|
|                           | Tivozanib<br>(n=173) | Sorafenib<br>(n=170) | Tivozanib<br>(n=259) | Sorafenib<br>(n=257) |
| Hypertension <sup>1</sup> |                      |                      |                      |                      |

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|              | TIVO-3   |          | TIVO-1    |          |
|--------------|----------|----------|-----------|----------|
| All grades   | 76 (44%) | 52 (31%) | 123 (48%) | 95 (37%) |
| Grade 3 or 4 | 42 (24%) | 28 (16%) | 72 (28%)  | 47 (18%) |

Source: ADAE.xpt (STUDYID, USUBJID, TRTEMFL, TRT01A, AEDECOD, AETOXGR). Data cutoff: May 1, 2020.

<sup>1</sup>Includes blood pressure increased, essential hypertension, hypertension, hypertensive crisis

Hypertension occurred in 454/1008 (45%) of patients with RCC treated with tivozanib at the proposed dose in the overall safety population, with 22% of the events > Grade 3. Median time to onset of hypertension was 2 weeks (range: 0 – 192 weeks).

One patient in TIVO-1 inadvertently overdosed, taking 3 x 1.5 mg capsules daily for 2 days (9 mg total) of tivozanib and experienced a death due to hypertension. Information about this death due to tivozanib overdose is included in section 5.1 of the tivozanib label.

Section 5.1, the Warning & Precaution for Hypertension, of labeling recommends providers to “Control blood pressure prior to treatment with FOTIVDA. Monitor blood pressure after 2 weeks and at least monthly thereafter during treatment with FOTIVDA,” consistent with the TIVO-3 protocol. Additionally, Section 2.2 recommends dose interruption followed by reduction for grade 3 hypertension not controlled by anti-hypertensive therapy, and permanent discontinuation for grade 4 hypertension, which is consistent with the TIVO-3 protocol as well.

### 8.2.5.2 Cardiac Failure

Cardiac failure occurred in 16/1008 (1.6%) of patients with RCC treated with tivozanib at the proposed dose in the overall safety population, with 10 (1.0%) events ≥ Grade 3, and 6 (0.6%) events were fatal. This made it the most common adverse event leading to death.

Both TIVO-1 and TIVO-3 excluded patients with significant cardiovascular disease, including symptomatic heart failure, uncontrolled hypertension, history of severe angina or acute coronary syndrome within 6 months prior, or serious/uncontrolled arrhythmia. In both trials, cardiac failure occurred at comparably low rates in the tivozanib vs. sorafenib arms.

|                              | TIVO-3               |                      | TIVO-1               |                      |
|------------------------------|----------------------|----------------------|----------------------|----------------------|
|                              | Tivozanib<br>(n=173) | Sorafenib<br>(n=170) | Tivozanib<br>(n=259) | Sorafenib<br>(n=257) |
| Cardiac failure <sup>1</sup> |                      |                      |                      |                      |
| All grades                   | 2 (1.2%)             | 4 (2.4%)             | 5 (1.9%)             | 4 (1.6%)             |
| Grade 3 or 4                 | 1 (0.6%)             | 0                    | 1 (0.4%)             | 2 (0.8%)             |

Source: ADAE.xpt (STUDYID, USUBJID, TRTEMFL, TRT01A, AEDECOD, AGRADE)

<sup>1</sup>Includes cardiac failure, cardiac failure acute, cardiac failure congestive, cardiopulmonary failure, ejection fraction decreased, left ventricular dysfunction, pulmonary edema, and ventricular hypokinesia.

### 8.2.5.3 Cardiac Ischemia and Arterial Thromboembolic Events

Cardiac ischemia occurred in 32/1008 (3.2%) of patients with RCC treated with tivozanib at the proposed dose in the overall safety population, with 15 (1.5%) events  $\geq$  Grade 3, and 4 (0.4%) events were fatal. Arterial thromboembolic events were reported in 20/1008 (2%) of patients, including 1 death due to ischemic stroke (0.1%).

Both TIVO-1 and TIVO-3 excluded patients with history of thromboembolic event (including peripheral ischemia  $\geq$  grade 2), severe angina or acute coronary syndrome within 6 months prior to first dose of study drug. In TIVO-3 trial, these events occurred in a slightly higher lower proportion of patients in the tivozanib compared to sorafenib arm. In TIVO-1, the events occurred at comparable rates across arms.

|                                                                     | TIVO-3               |                      | TIVO-1               |                      |
|---------------------------------------------------------------------|----------------------|----------------------|----------------------|----------------------|
|                                                                     | Tivozanib<br>(n=173) | Sorafenib<br>(n=170) | Tivozanib<br>(n=259) | Sorafenib<br>(n=257) |
| Cardiac Ischemia and/or Arterial Thromboembolic Events <sup>1</sup> |                      |                      |                      |                      |
| All grades                                                          | 6 (3.5%)             | 10 (5.9%)            | 12 (4.6%)            | 9 (3.5%)             |
| Grade 3 or 4                                                        | 4 (2.3%)             | 7 (4.1%)             | 7 (2.7%)             | 8 (3.1%)             |

Source: ADAE.xpt (STUDYID, USUBJID, TRTEMFL, TRT01A, AEDECOD, AETOXGR). Data cutoff: May 1, 2020.

<sup>1</sup>Includes acute coronary syndrome, acute myocardial infarction, ischaemic stroke, myocardial infarction, myocardial ischaemia, peripheral artery thrombosis, retinal artery thrombosis, thrombotic cerebral infarction, transient ischemic attack

In TIVO-3, of the 11 patients (in either treatment arm) who had grade 3-4 cardiac ischemia or thromboembolic event, 6 patients had baseline borderline high blood pressure (sBP between 140 and 150 mmHg or dBP between 90 and 100 mmHg.)

### 8.2.5.4 Venous Thromboembolic Events

Venous thromboembolic events occurred in 24/1008 (2.4%) of patients with RCC treated with tivozanib at the proposed dose in the overall safety population, with 13 (1.3%) events  $\geq$  Grade 3, and 3 (0.3%) events were fatal.

Both TIVO-1 and TIVO-3 excluded patients with history of thromboembolic event within 6 months prior to first dose of study drug. Overall, the rates of venous thromboembolic events were slightly higher in the tivozanib arm compared to sorafenib.

|                                           | TIVO-3               |                      | TIVO-1               |                      |
|-------------------------------------------|----------------------|----------------------|----------------------|----------------------|
|                                           | Tivozanib<br>(n=173) | Sorafenib<br>(n=170) | Tivozanib<br>(n=259) | Sorafenib<br>(n=257) |
| Venous Thromboembolic Events <sup>1</sup> |                      |                      |                      |                      |
| All grades                                | 7 (4.0%)             | 6 (3.5%)             | 6 (2.3%)             | 2 (0.8%)             |
| Grade 3 or 4                              | 5 (2.9%)             | 0                    | 1 (0.4%)             | 0                    |

Source: ADAE.xpt (STUDYID, USUBJID, TRTEMFL, TRT01A, AEDECOD, AETOXGR). Data cutoff: May 1, 2020.

<sup>1</sup>Includes pulmonary embolism, deep vein thrombosis, vena cava thrombosis, pelvic venous thrombosis, subclavian vein thrombosis, thrombophlebitis, venous thrombosis

### 8.2.5.5 Hemorrhagic Events

Hemorrhagic events occurred in 113/1008 (11%) of patients with RCC treated with tivozanib at the proposed dose in the overall safety population, with 19 (1.9%) events  $\geq$  Grade 3, and 2 (0.2%) events were fatal.

Both TIVO-1 and TIVO-3 excluded patients with history of Grade  $\geq$  2 bleeding (hematemesis, hematochezia, hemoptysis, hematuria, etc.) within 6 months prior to first dose. In both trials, the proportion of patients with bleeding events was higher in the tivozanib arm than in the sorafenib arm.

|                                 | TIVO-3               |                      | TIVO-1               |                      |
|---------------------------------|----------------------|----------------------|----------------------|----------------------|
|                                 | Tivozanib<br>(n=173) | Sorafenib<br>(n=170) | Tivozanib<br>(n=259) | Sorafenib<br>(n=257) |
| Hemorrhagic Events <sup>1</sup> |                      |                      |                      |                      |
| All grades                      | 30 (17%)             | 21 (12%)             | 32 (12%)             | 15 (5.8%)            |
| Grade 3 or 4                    | 5 (2.9%)             | 2 (1.2%)             | 7 (2.7%)             | 2 (0.8%)             |

Source: ADAE.xpt (STUDYID, USUBJID, TRTEMFL, TRT01A, AEDECOD, AETOXGR). Data cutoff: May 1, 2020.

<sup>1</sup>Includes anal hemorrhage, aortic aneurysm rupture, astringent therapy, cervix hemorrhage uterine, contusion, epistaxis, gastrointestinal hemorrhage, gingival bleeding, hematemesis, hematochezia, hematoma, hematuria, hemoptysis, hemorrhage intracranial, hemorrhagic erosive gastritis, hemorrhagic stroke, hemorrhoidal hemorrhage, injection site hemorrhage, petechiae, postmenopausal hemorrhage, purpura, rectal hemorrhage, retinal hemorrhage, small intestinal hemorrhage

### 8.2.5.6 Proteinuria

Proteinuria occurred in 81/1008 (8%) of patients with RCC treated with tivozanib at the proposed dose in the overall safety population, with 20 (2%) Grade 3 events, and no Grade  $\geq$  4 events. There were no nephrotic syndrome events reported. Of the 81 patients with proteinuria, only 3 patients developed acute kidney injury (defined as acute kidney injury, anuria, azotemia, oliguria, or renal failure). Thus, there is lack of strong evidence that proteinuria is prognostic of deterioration in renal function.

Both TIVO-1 and TIVO-3 monitored for proteinuria by requiring a urinalysis on day 1 of every cycle; if urinalysis dipstick showed protein 4+, a 24-hour urine collection was required. In TIVO-3, the proportion of patients with proteinuria was higher in the tivozanib arm than in the sorafenib arm. In TIVO-1, rates of proteinuria were comparable across treatment arms.

|  | TIVO-3               |                      | TIVO-1               |                      |
|--|----------------------|----------------------|----------------------|----------------------|
|  | Tivozanib<br>(n=173) | Sorafenib<br>(n=170) | Tivozanib<br>(n=259) | Sorafenib<br>(n=257) |
|  |                      |                      |                      |                      |

|                          | TIVO-3    |          | TIVO-1    |           |
|--------------------------|-----------|----------|-----------|-----------|
| Proteinuria <sup>1</sup> |           |          |           |           |
| All grades               | 16 (9.2%) | 7 (4.1%) | 24 (9.3%) | 22 (8.6%) |
| Grade 3 or 4             | 4 (2.3%)  | 3 (1.8%) | 4 (1.5%)  | 7 (2.7%)  |

Source: ADAE.xpt (STUDYID, USUBJID, TRTEMFL, TRT01A, AEDECOD, AETOXGR). Data cutoff: May 1, 2020.

<sup>1</sup>Includes protein urine present, proteinuria

### 8.2.5.7 Thyroid Dysfunction

Hypothyroidism occurred in 115/1008 (11%) of patients with RCC treated with tivozanib at the proposed dose in the overall safety population, with 3 (0.3%) Grade 3 events and no Grade ≥ 4 events. Hyperthyroidism occurred in 1% of patients.

Both TIVO-1 and TIVO-3 monitored for thyroid dysfunction by requiring thyroid function tests on day 1 of every cycle. In both trials, the proportion of patients with hypothyroidism events in the tivozanib arm compared to the sorafenib arm is more than double (24% vs. 11% and 10% vs. 4.3%). Additionally, the risk of hypothyroidism appears to increase by more than two-fold from the first-line setting to the third-line setting (from 10% to 24% among tivozanib-treated patients, and from 4% to 11% among sorafenib-treated patients). This suggests residual treatment effects from earlier lines of therapy.

|                              | TIVO-3               |                      | TIVO-1               |                      |
|------------------------------|----------------------|----------------------|----------------------|----------------------|
|                              | Tivozanib<br>(n=173) | Sorafenib<br>(n=170) | Tivozanib<br>(n=259) | Sorafenib<br>(n=257) |
| Hypothyroidism <sup>1</sup>  |                      |                      |                      |                      |
| All grades                   | 41 (24%)             | 18 (11%)             | 27 (10.4%)           | 11 (4.3%)            |
| Grade 3 or 4                 | 1 (0.6%)             | 0                    | 0                    | 0                    |
| Hyperthyroidism <sup>2</sup> |                      |                      |                      |                      |
| All grades                   | 6 (3.5%)             | 4 (2.4%)             | 5 (1.9%)             | 4 (1.6%)             |
| Grade 3 or 4                 | 0                    | 0                    | 1 (0.4%)             | 0                    |

Source: ADAE.xpt (STUDYID, USUBJID, TRTEMFL, TRT01A, AEDECOD, AETOXGR). Data cutoff: May 1, 2020.

<sup>1</sup>Includes blood thyroid stimulating hormone increased, hypothyroidism

<sup>2</sup>Includes blood thyroid stimulating hormone decreased, hyperthyroidism, thyroxine free increased, toxic nodular goitre

### 8.2.5.8 Risk of Impaired Wound Healing

Among the 1008 patients with RCC treated with tivozanib at the proposed dose in the overall safety population, no reports of impaired wound healing were reported. The sponsor has not conducted any formal studies to characterize the risk of impaired wound healing. However, the Office of Oncologic Diseases (OOD) has decided that all drugs claiming anti-VEGF inhibition activity should state a duration of time for wound healing to hold the drug prior to surgery and the time to resume the drug postoperatively in the Warnings & Precautions section. The rationale is to provide consistent and proportional communication across drug products regarding adverse reactions related to VEGF pathway antagonism.

After multi-disciplinary discussion, in the absence of clinical data, OOD's policy is to recommend withholding the drug for 5 half lives prior to scheduled surgery and for 2 weeks (and after clinical assessment of adequate wound healing) after surgery.

The half-life of tivozanib is 111 hours. Therefore, the recommendation per labeling is to hold tivozanib for 24 days prior to major surgery.

#### 8.2.5.9 Reversible Posterior Leukoencephalopathy Syndrome

Reversible posterior leukoencephalopathy syndrome (RPLS, also known as PRES), a syndrome of subcortical vasogenic edema diagnosed by MRI, has been reported in association with drugs inhibiting the VEGF pathway.[22] It is unclear if this syndrome occurred in patients treated with tivozanib due to lack of diagnostic imaging with MRI. However, due to the potential risk of RPLS, section 6.1 of tivozanib labeling includes the sentence, "Clinically relevant adverse reactions in < 15% of patients who received FOTIVDA included ... delirium."

The sponsor reported all patients with "Non-Infectious Encephalopathy" as potential RPLS cases. These included Preferred Terms of delirium, encephalopathy, or toxic encephalopathy. The proportion of patients with non-infectious encephalopathy was similarly low in either treatment arm in both TIVO-1 and TIVO-3 (1% in each arm in each trial).

#### 8.2.5.10 Allergic Reactions to Tartrazine (FD&C Yellow No.5)

The 0.89 mg tivozanib (equivalent to 1.0 mg tivozanib hydrochloride) capsule contains FD&C Yellow No.5 (tartrazine) as an imprint ink which may cause allergic-type reactions (including bronchial asthma) in certain susceptible patients. Although the overall incidence of FD&C Yellow No.5 (tartrazine) sensitivity in the general population is low, it is frequently seen in patients who also have aspirin hypersensitivity.

FDA requested the sponsor to conduct a risk assessment of "your perception of risk associated with tartrazine in tivozanib. This should include a review of your global safety database of allergic reactions to the tartrazine in tivozanib. You should also generally provide your assessment overall of this risk."

The sponsor performed a comprehensive cumulative review of the global safety database representing patient exposure corresponding to 1,064 patient-years with commercial product from the date of European Union approval (August 24, 2017) through November 23, 2020 for any suspicion of allergic reactions to the tartrazine in tivozanib. Cumulatively through November 23, 2020, there were a total of 10 events, the symptoms of which, while non-specific, could be part of a hypersensitivity reaction. These events were reported as (1-2 events each) mouth swelling, chills, peripheral swelling, pruritis, rash, skin necrosis, and skin ulcer.

There were no reports of anaphylaxis nor urticaria, and the events reported did not appear to suggest allergic reactions. The sponsor concluded that the risk of allergic reaction was low.

FDA agrees that the risk of allergic reaction due to tartrazine sensitivity is low. Among the 1008 patients with RCC treated with tivozanib at the proposed dose in the overall safety population, 141 (14%) of patients potentially had an allergic reaction. AE terms related to rash comprised most of these "allergic reactions." Only 1 patient of 1008 had wheezing, which was Grade 1-2, and none had asthma. Similarly, in TIVO-3, 16% of patients had potential allergic reactions (dermatitis, dermatitis acneiform, drug eruption, erythema, erythema multiforme, photosensitivity reaction, pruritus, rash, rash erythematous, rash generalised, rash macular, rash maculo-papular, rash morbilliform, rash pruritic, skin exfoliation, swelling face, toxic skin eruption, urticaria), with two Grade 3 events and no Grade  $\geq$  4 events. In contrast, 50% of patients in the sorafenib arm had allergic reactions (again, mostly rash), with 15% Grade 3. The only patient in TIVO-3 who had wheezing was in the sorafenib arm.

See also Skin Reactions below.

#### 8.2.5.11 Skin Reactions

Skin reactions are not included in the Warnings and Precautions section of the tivozanib labeling, but are a known adverse effect of kinase inhibitors. The proportion of patients with skin reactions in TIVO-3 and TIVO-1 was noticeably lower in the tivozanib arms compared to the sorafenib arms. The difference was accentuated in the rate of grade 3-4 rash in TIVO-3 (15% vs. 5.1%), which may underscore the additive effects of kinase inhibitors used in sequence that have overlapping dermatologic toxicities.

|                                            | TIVO-3               |                      | TIVO-1               |                      |
|--------------------------------------------|----------------------|----------------------|----------------------|----------------------|
|                                            | Tivozanib<br>(n=173) | Sorafenib<br>(n=170) | Tivozanib<br>(n=259) | Sorafenib<br>(n=257) |
| Rash <sup>1</sup>                          |                      |                      |                      |                      |
| All grades                                 | 31 (18%)             | 88 (52%)             | 36 (14%)             | 88 (34%)             |
| Grade 3 or 4                               | 2 (1.2%)             | 26 (15%)             | 5 (1.9%)             | 13 (5.1%)            |
| Palmar-plantar erythrodysesthesia syndrome |                      |                      |                      |                      |
| All grades                                 | 28 (16%)             | 69 (41%)             | 36 (14%)             | 139 (54%)            |
| Grade 3 or 4                               | 2 (1.2%)             | 17 (10%)             | 5 (1.9%)             | 43 (17%)             |

Source: ADAE.xpt (STUDYID, USUBJID, TRTEMFL, TRT01A, AEDECOD, AETOXGR). Data cutoff: May 1, 2020.

<sup>1</sup>Includes acne, dermatitis, dermatitis acneiform, dermatitis allergic, dermatitis bullous, dermatitis contact, dermatitis exfoliative, drug eruption, eczema, eczema asteatotic, eczema nummular, erythema, erythema multiforme, generalized erythema, hidradenitis, papule, petechiae, photosensitivity reaction, pruritus, psoriasis, rash, rash erythematous, rash generalised, rash macular, rash maculo-papular, rash morbilliform, rash papulosquamous, rash pruritic, seborrheic dermatitis, skin exfoliation, skin irritation, skin lesion, swelling face, toxic skin eruption, urticaria

**Reviewer comment:** Skin reactions, especially palmar-plantar erythrodysesthesia syndrome, is one of the chronic toxicities that can commonly affect patients on this class of therapy. We note

*the overall lower rate of these reactions in tivozanib vs. sorafenib, and that this likely contributes to a more favorable toxicity profile in this regard.*

#### 8.2.5.12 Aneurysm or Artery Dissection

Aneurysm or Artery Dissection is not a Warning/Precaution in tivozanib labeling. Among the 1008 patients with RCC treated with tivozanib at the proposed dose in the overall safety population, aneurysm or artery dissection occurred in 3 patients. One of the events was grade 1-2 (aortic dilatation), one was grade 3 (aortic aneurysm, in a patient that was treated in TIVO-1 on the sorafenib arm and then crossed over to tivozanib) and one of the events was grade 5 (aortic aneurysm rupture). Since determination of causality was confounded in the grade 3 event, the amount of data to justify a separate Warning & Precaution for Aneurysm or Artery Dissection was sparse. The review team decided to include the grade 5 event in the Hemorrhagic Events category.

#### 8.2.5.13 Osteonecrosis

Osteonecrosis is not a Warning/Precaution in tivozanib labeling. Among the 1008 patients with RCC treated with tivozanib at the proposed dose in the overall safety population, osteonecrosis occurred in 3 patients. All events were grade 1-2. However, osteonecrosis has been reported in association with drugs inhibiting the VEGF pathway, and is included in the Warnings & Precautions of some drug labels. Therefore, section 6.1 of tivozanib labeling includes the sentence, "Clinically relevant adverse reactions in < 15% of patients who received FOTIVDA included ... osteonecrosis..."

#### 8.2.5.14 Gastrointestinal Fistula/Perforation

Gastrointestinal fistula or perforation is not a Warning/Precaution in tivozanib labeling. These AEs have been reported following initiation of treatment with other VEGF-targeting drugs. Among the 1008 patients with RCC treated with tivozanib at the proposed dose in the overall safety population, gastrointestinal fistula occurred in 1 patient, which was grade 4. No patients had perforations. Both TIVO-1 and TIVO-3 excluded patients with active peptic ulcer disease, inflammatory bowel disease, ulcerative colitis, or other gastrointestinal condition with increased risk of perforation; history of abdominal fistula, gastrointestinal perforation, or intra-abdominal abscess within 4 weeks prior to first dose of study drug.

### **8.2.6 Clinical Outcome Assessment (COA) Analyses Informing Safety/Tolerability**

The sponsor did not collect any patient-reported outcome (PRO) data in TIVO-3. However, the sponsor did collect PRO data in TIVO-1, which was a randomized trial with the same treatment regimens administered in TIVO-3, tivozanib versus sorafenib. FDA therefore requested the

sponsor to provide PRO analyses in an effort to understand the patient experience with tivozanib in comparison to sorafenib.

Specifically, FDA requested data from TIVO-1 summarizing results from the PRO questionnaire The Functional Assessment of Cancer Therapy - General (FACT-G) (FACT-G), including questionnaire completion rates and item-level analyses for the first 6 months for items assessing treatment side effects.

The FDA Oncology Center of Excellence Patient-Focused Drug Development group reviewed the analyses and provided the following interpretation

- Completion rate was quite good in both arms.
- No definitive conclusion could be drawn based on item GP1 results (lack of energy).
- GP5 results show that patients randomized to sorafenib reported worse overall side effect bother.

## 8.2.7 Safety Analyses by Demographic Subgroups

The demographic subgroup analyses below address sex, age and race in the overall safety population (n=1008) and in the primary safety population (TIVO-3).

### 8.2.7.1 Sex

**Table 31. Safety Results in TIVO-3 by Sex**

|              | Male                 |                      | Female              |                     |
|--------------|----------------------|----------------------|---------------------|---------------------|
|              | Tivozanib<br>(n=125) | Sorafenib<br>(n=123) | Tivozanib<br>(n=48) | Sorafenib<br>(n=47) |
| All grades   | 124 (99%)            | 92 (100%)            | 47 (98%)            | 47 (100%)           |
| Grade 3 or 4 | 81 (65%)             | 93 (76%)             | 34 (71%)            | 30 (64%)            |
| Grade 5      | 12 (9.6%)            | 10 (8.1%)            | 5 (10%)             | 4 (8.5%)            |

Source: ADAE.xpt (STUDYID, USUBJID, SEX, TRTEMFL, TRT01A, AEDECOD, AETOXGR). Data cutoff: May 1, 2020.

Male patients had slightly lower rates of grade 3-4 events on tivozanib than sorafenib. Female patients had slightly higher rates of grade 3-4 events on tivozanib than sorafenib.

Similarly, within the tivozanib treatment arm, **female** patients had slightly higher rates of grade 3-4 events than male patients (71 vs. 65%); within the sorafenib treatment arm, the opposite was true (**male** patients had slightly higher rates of grade 3-4 events, 76% vs. 64%). This exploratory analysis is limited by the relatively small number of patients in TIVO-3.

### 8.2.7.2 Age

Of the patients with advanced RCC treated with tivozanib in the overall safety population, 297/1008 (29%) were ≥ 65 years of age and 4% were ≥ 75 of age. While the proportions of patients with adverse events were higher in the < 65-year-olds compared to the ≥ 65-year-olds (any grade, grade 3-4, and grade 5 [Table... below]), the differences were small and no patterns for specific adverse events that differed by age group were clearly seen. Additionally, the increase in grade 3-4 events with increasing age was more marked in the sorafenib arm (Table--).

**Table 32. Safety Results by Age in Overall Safety Population (n=1008)**

|           | Tivozanib (n=1008)        |                           |
|-----------|---------------------------|---------------------------|
|           | < 65 years old<br>(n=631) | ≥ 65 years old<br>(n=297) |
| Any TEAE  | 631 (89%)                 | 285 (96%)                 |
| Grade 3-4 | 348 (49%)                 | 173 (58%)                 |
| Grade 5   | 56 (7.9%)                 | 125 (8.4%)                |

Source: ADAE.xpt (STUDYID, USUBJID, AGEGR, TRTEMFL, TRT01A, AEDECOD, AETOXGR). Data cutoff: May 1, 2020.

Of the 175 patients randomized to tivozanib in TIVO-3, 44% were ≥ 65 years of age and 9% were ≥ 75 of age.

**Table 33. Safety Results in TIVO-3 in Patients ≥ 65 and Patients < 65 Years of Age**

|              | < 65 years of age   |                     | ≥ 65 years of age    |                      |
|--------------|---------------------|---------------------|----------------------|----------------------|
|              | Tivozanib<br>(n=97) | Sorafenib<br>(n=92) | Tivozanib<br>(n=259) | Sorafenib<br>(n=257) |
| All grades   | 95 (98%)            | 92 (100%)           | 76 (100%)            | 78 (100%)            |
| Grade 3 or 4 | 60 (62%)            | 56 (61%)            | 55 (72%)             | 67 (86%)             |
| Grade 5      | 11 (11%)            | 10 (11%)            | 6 (7.9%)             | 4 (5.1%)             |

Source: ADAE.xpt (STUDYID, USUBJID, AGEGR, TRTEMFL, TRT01A, AEDECOD, AETOXGR). Data cutoff: May 1, 2020.

### 8.2.7.3 Race

The low numbers of non-White patients enrolled in TIVO-1 and TIVO-3 precluded meaningful comparison of safety across races within trials (≤10 patients of each non-White race per arm per trial [and in TIVO-3 specifically, ≤2 patients of each non-White race]). In the overall safety population, the low numbers of non-White or non-Asian patients also precluded meaningful comparison of safety across races within patients who had received tivozanib (black, n=7; not reported/other/unknown, n=11). The table below compares safety in patients who self-identified as Asian compared to those who self-identified as White in the overall safety population.

**Table 34. Safety Results in Overall Safety Population (n=1008): White and Asian Races**

|              | <b>White<br/>(n=951)</b> | <b>Asian<br/>(n=39)</b> |
|--------------|--------------------------|-------------------------|
| All grades   | 861 (91%)                | 37 (95%)                |
| Grade 3 or 4 | 486 (51%)                | 20 (51%)                |
| Grade 5      | 80 (8%)                  | 2 (5%)                  |

Source: ADAE.xpt (STUDYID, USUBJID, RACE, TRTEMFL, TRT01A, AEDECOD, AETOXGR). Data cutoff: May 1, 2020.

While there is insufficient data to draw conclusions on the impact of race on the safety profile of tivozanib, the data available for Asian patients suggests overall that the tolerability of tivozanib is comparable to the tolerability in White patients. The table below highlights the higher incidence of rash and palmar-plantar erythrodysesthesia in Asian patients compared to the incidence in White patients (both all-grade and grades 3-4). Other specific AEs occurred in similar proportions of patients across these 2 racial groups.

|                                   | <b>White<br/>(n=951)</b> |                     | <b>Asian<br/>(n=39)</b> |                     |
|-----------------------------------|--------------------------|---------------------|-------------------------|---------------------|
|                                   | <b>All grades</b>        | <b>Grade 3 or 4</b> | <b>All grades</b>       | <b>Grade 3 or 4</b> |
| Rash <sup>1</sup>                 | 134 (14%)                | 6 (0.6%)            | 15 (38%)                | 3 (7.7%)            |
| Palmar-plantar erythrodysesthesia | 110 (12%)                | 11 (1.1%)           | 8 (21%)                 | 3 (7.7%)            |

<sup>1</sup>Includes acne, dermatitis, dermatitis acneiform, dermatitis bullous, dermatitis allergic, dermatitis contact, dermatitis exfoliative, exfoliative rash, eczema, eczema nummular, erythema, erythema multiforme, generalised erythema, hidradenitis, papule, perivascular dermatitis, petechiae, photosensitivity reaction, pruritus, pruritus generalised, psoriasis, purpura, rash, rash erythematous, rash generalised, rash macular, rash maculo-papular, rash papular, rash papulosquamous, rash pruritic, rash vesicular, skin exfoliation, skin lesion, swelling face, urticaria

**Reviewer comment:** Blacks were under-represented in the demographics of TIVO-3 (n=2, both in the sorafenib arm) vs the expected numbers based on the U.S. population. The incidence of kidney and renal pelvis cancers is highest among Black men (24.7 per 100,000), followed by White men (22.0 per 100,000).[23] As noted by Sims et al,[23] “In the United States, White populations have the lowest prevalence of RCC compared to other ethnic groups, while Black Americans suffer disproportionately from the adverse effects of RCC.. During the past two decades, the incidence rate of RCC has significantly declined among Caucasians but has rapidly increased among African Americans... A disparity in relative survival still persists between African Americans and Caucasians patients with kidney cancer even when controlling for treatment and other prognostic factors including stage, tumor size, and grade... The cause of this disparity in mortality is unknown.” Possible factors include tumor genomic differences which may predict different responsiveness to therapy.[24]

During the ODAC for TIVO-1, the underrepresentation of Black patients was discussed: “Another committee member questioned the limited exposure data in African American patients,

***describing these patients as having unique needs in the areas of kidney cancer and hypertension.”***

*FDA has reminded sponsors that racial and ethnic minorities should be represented appropriately in clinical trials. FDA consistently advises sponsors to ensure that clinical trial sites include geographic locations with a higher concentration of racial and ethnic minorities to recruit a diverse study population, referring them to the Guidance for Industry: Clinical Trial Populations — Eligibility Criteria, Enrollment Practices, and Trial Designs at <https://www.fda.gov/media/127712/download>*

## **8.2.8 Specific Safety Studies/Clinical Trials**

The sponsor conducted a hepatic impairment study (AV-951-12-118) between in hepatically impaired patients and matched normal controls, both without cancer, using the Child-Pugh categories of hepatic impairment, between August 2012 and September 2013. After a 10-hour fast, 44 patients received 1 dose of 1.5 mg tivozanib hydrochloride. Pharmacokinetic results are described in Section 19.4 (OCP Appendices).

Overall, 11/22 (50%) of patients with hepatic impairment and 5/22 (23%) of patients with normal hepatic function at baseline had TEAEs. The highest grade TEAEs were two grade 3 AEs of hypertension, one in a patient with moderate hepatic impairment and one in a patient with severe hepatic impairment. Hypertension was also the most common TEAE in the entire study, occurring in 25-37.5% (of 8 patients enrolled in each of the mild and moderate hepatic impairment groups, and 6 patients in the severe hepatic impairment group) of patients with mild, moderate, or severe hepatic impairment, and in 23% of patients with normal hepatic function.

In conjunction with the pharmacokinetic results, these findings support the recommendation in labeling to adjust the dosage in patients with moderate hepatic impairment and avoid use in patients with severe hepatic impairment.

## **8.2.9 Additional Safety Explorations**

### **Human Carcinogenicity or Tumor Development**

N/A

### **Human Reproduction and Pregnancy**

N/A

### **Pediatrics and Assessment of Effects on Growth**

N/A

### **Overdose, Drug Abuse Potential, Withdrawal, and Rebound**

No specific studies for overdose, drug abuse potential, withdrawal, or rebound are relevant for this application.

Two patients in TIVO-3 overdosed on tivozanib due to patient error. The first patient took 32 days of tivozanib continuously without interruption, and suffered no adverse event related to the exposure. The second patient took two capsules on the same day in cycle 1, Day 1. The patient experienced a Grade 2 hypertension which lasted 5 days and then resumed tivozanib.

One patient in TIVO-1 overdosed due to patient error, which is described in Section 8.2.5.1.

### **8.2.10 Safety in the Postmarket Setting**

#### **Safety Concerns Identified Through Postmarket Experience**

No safety concerns have been identified through postmarket experience. FDA specifically requested the sponsor provide postmarket data regarding potential allergic reactions (described in Section 8.2.5.10) and safety data in patients with severe renal impairment.

The sponsor identified no additional safety data through a search of postmarket experience in Europe from the time of EU approval (August 2017) through February 23, 2020.

FDA also requested the sponsor to provide any additional postmarket safety data in patients with severe renal impairment. The sponsor stated that there were no additional postmarketing safety reports in this population. Although no patients with severe renal impairment (CrCl 15-29 mL/min) were enrolled in TIVO-3, FDA ultimately decided that no dosage modification is recommended for patients with mild to severe renal impairment. This was due to lack of change in PK/exposure in patients with severe renal impairment (see Clinical Pharmacology section), relatively low renal excretion of the drug, and lack of extraordinary toxicity in the 2 patients with borderline severe renal impairment in TIVO-1.

#### **Expectations on Safety in the Postmarket Setting**

TIVO-3 excluded patients with several baseline factors that might be expected to raise the likelihood of developing adverse events, including ECOG performance status  $\geq 2$ , serum creatinine  $> 1.5 \times$  ULN, untreated brain metastases, cardiovascular disease, poorly-controlled hypertension, and history of recent thromboembolism. The use of tivozanib in these patients could constitute a safety concern in the postmarketing setting. However, risk mitigation for many of these comorbidities is addressed in labeling, and FDA has not identified a relevant

scientific question that would be effectively answered using postmarket data. Thus, FDA has not required the sponsor to conduct additional postmarket safety studies.

### **8.2.11 Integrated Assessment of Safety**

FDA's integrated assessment of safety focused on the 1008 patients with RCC who received the proposed dose of tivozanib. The risks associated with tivozanib in this overall safety population are described in section 8.2.5, Analysis of Submission-Specific Safety Issues. The safety profile in the overall safety population was generally similar to the safety profile in TIVO-3, with the exception of thyroid dysfunction. Patients who were not treated in one of the phase 3 trials (TIVO-1 or TIVO-3) likely were not monitored with thyroid function tests as closely and did not have as much exposure to study drug, which may explain the higher rates of thyroid dysfunction in tivozanib-treated patients in TIVO-1 and TIVO-3 compared to the other patients in the overall safety population.

The safety profile of tivozanib was adequately assessed in the submitted database. At minimum, the toxicity was within range for this patient population, with adverse reactions manageable with dose reduction, temporary treatment discontinuation, and/or standard medical care. In fact, the lower rates of dose reduction, interruption, or permanent discontinuation, supported by the overall treatment bother results from analyses of TIVO-1 PRO results, demonstrate a likely overall improved tolerability over an accepted standard-of-care according to several clinically relevant metrics. Furthermore, the toxicity profile is consistent with other drugs affecting the VEGF pathway, which increases the familiarity of providers with risk management practices in this patient population.

## **8.3 Statistical Issues**

The FDA efficacy evaluation was based on data from the TIVO-3 study. Study TIVO-3 met its primary objective of PFS per BIRC assessment. The PFS results were consistent across sensitivity analyses, and no outliers were observed in the subgroup analyses. In addition, no apparent detrimental effect of tivozanib on survival was observed. There are no major statistical issues with this application.

## **8.4 Conclusions and Recommendations**

The review team recommends regular approval for tivozanib. Tivozanib 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. Overall, the similar efficacy observed between tivozanib and sorafenib in TIVO-3, treatment with tivozanib at the recommended dose will provide an additional treatment option for patients with relapsed or refractory RCC following at least 2 prior lines of therapy. The benefit to patients and providers of an additional treatment alternative is augmented by the slightly different toxicity profile of

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{FOTIVDA, tivozanib}

tivozanib in comparison to other approved treatments for this patient population, including lower rates of diarrhea and skin reactions, potentially better overall tolerability, and the unmet need in third-line RCC.

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{FOTIVDA, tivozanib}

X

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Lijun Zhang, PhD  
Primary Statistical Reviewer

X

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Mallorie Fiero, PhD  
Statistical Team Leader

X

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Elaine Chang, MD  
Primary Clinical Reviewer

X

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Chana Weinstock, MD  
Clinical Team Leader

## **9 Advisory Committee Meeting and Other External Consultations**

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No ODAC was convened for this application.

## 10 Pediatrics

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From Oncology Subcommittee of PeRC Meeting Minutes dated February 10, 2021:

Proposed Indication: Treatment of patients with relapsed or refractory renal cell carcinoma

Planned waiver justification: Necessary studies are impossible or highly impracticable to conduct in the pediatric population.

OCE PeRC Recommendations:

The OCE PeRC concurred with the Division's agreement with the sponsor's request for a full waiver of pediatric studies.

## 11 Labeling Recommendations

### 11.1 Prescription Drug Labeling

| Summary of Significant Labeling Changes (High level changes and not direct quotations) |                                                                                                                                        |                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
|----------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Section                                                                                | Proposed Labeling                                                                                                                      | Approved Labeling<br>(As of February 15, 2021)                                                                                                                                                                                                                                                                                                                                                                                                       |
| <b>Highlights</b>                                                                      |                                                                                                                                        |                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
| (N/A)                                                                                  | FOTIVDA® (tivozanib hydrochloride)                                                                                                     | FDA revised to “ <b>FOTIVDA® (tivozanib)</b> ” because new salt drug products should consult the General Chapter <1121> discussion of USP’s naming policy for such drug products.                                                                                                                                                                                                                                                                    |
| Indications and Usage                                                                  | FOTIVDA is a kinase inhibitor indicated for the treatment of patients with relapsed or refractory advanced renal cell carcinoma (RCC). | FDA revised to “indicated for the treatment of <b>adult</b> patients with <b>advanced</b> relapsed or refractory advanced renal cell carcinoma (RCC) <b>with disease progression on or after two or more prior lines of therapy.</b> ” Additions of “adult” and “advanced” were for consistency with OOD Best Labeling Practices. “... progression on or after two or more prior lines...” was added for consistency with TIVO-3 patient population. |
| Dosage and Administration                                                              | 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)     | FDA added “until disease progression of unacceptable toxicity” for consistency with TIVO-3 protocol.                                                                                                                                                                                                                                                                                                                                                 |
| Warnings and Precautions                                                               | See Full Prescribing Information below.                                                                                                | See Full Prescribing Information below.                                                                                                                                                                                                                                                                                                                                                                                                              |
| <b>Full Prescribing Information</b>                                                    |                                                                                                                                        |                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
| 1 Indications and Usage                                                                | FOTIVDA is a kinase inhibitor indicated for the treatment of patients with relapsed or refractory advanced renal cell carcinoma (RCC). | See above (Highlights)                                                                                                                                                                                                                                                                                                                                                                                                                               |
| 2.1 Recommended Dosing                                                                 | The recommended dosage of FOTIVDA is one                                                                                               | Added a separate, 2-sentence paragraph with administration instructions consistent                                                                                                                                                                                                                                                                                                                                                                   |

|                                                 |                                                                                                                                                                                                                                                                                       |                                                                                                                                                                                                                                                                                                                                                             |
|-------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                                 | 1.34 mg capsule taken orally once daily with or without food...                                                                                                                                                                                                                       | with the PPI.                                                                                                                                                                                                                                                                                                                                               |
| 2.2 Dose Modifications for Adverse Reactions    | Patients Undergoing Surgery                                                                                                                                                                                                                                                           | Moved information regarding holding tivozanib perioperatively to Section 5.7.                                                                                                                                                                                                                                                                               |
| 2.2 Dose Modifications for Adverse Reactions    | Patients with Hepatic Impairment                                                                                                                                                                                                                                                      | Moved to Section 2.3 for consistency with OOD best labeling practices                                                                                                                                                                                                                                                                                       |
| 2.2 Dose Modifications for Adverse Reactions    | Table 1. Dosage Modifications for FOTIVDA                                                                                                                                                                                                                                             | Changed to “Dosage Modifications for Adverse Reactions” and added or modified several dose modification criteria for consistency with TIVO-3 protocol and other labeling for drugs affecting the VEGF pathway.                                                                                                                                              |
| 2.3 Dosage Modifications                        | Dosage Modifications for Use with a Concomitant Strong CYP3A4 Inducer                                                                                                                                                                                                                 | Deleted this section because it was covered in Section 7 and not required in Section 2.                                                                                                                                                                                                                                                                     |
| 2.3 Dosage Modifications for Hepatic Impairment | For moderate hepatic impairment... (b) (4)                                                                                                                                                                                                                                            | Removed the sentence (b) (4)<br>Changed dose modification instruction for moderate hepatic impairment to <b>0.89 mg daily for 21 days.</b>                                                                                                                                                                                                                  |
| 5 Warnings and Precautions (headings and order) | 5.1 Hypertension<br>5.2 Arterial and Venous Thrombotic Events<br>5.3 Hemorrhagic Events<br>5.4 Cardiac Failure<br>5.5 Thyroid Dysfunction<br>5.6 Proteinuria<br>5.7 Wound Healing Complications<br>5.8 Reversible Posterior Leukoencephalopathy Syndrome<br>5.9 Embryo-fetal Toxicity | 5.1 Hypertension and Hypertensive Crisis<br>5.2 Cardiac Failure<br>5.3 Cardiac Ischemia and Arterial Thrombotic Events<br>5.4 Venous Thromboembolic Events<br>5.4 Hemorrhagic Events<br>5.5 Proteinuria<br>5.6 Thyroid Dysfunction<br>5.7 Wound Healing Complications<br>5.8 Reversible Posterior Leukoencephalopathy Syndrome<br>5.9 Embryo-fetal Toxicity |
| 5 Warnings and Precautions                      | 5.1 Hypertension                                                                                                                                                                                                                                                                      | Added sentence about a patient who died due to hypertension following overdose. Added additional risk mitigation strategies consistent with protocol (monitoring blood pressure after 2 weeks and at least                                                                                                                                                  |

|                            |                                                                                                 |                                                                                                                                                                                                                                                                                                                                                                                                                                      |
|----------------------------|-------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                            |                                                                                                 | monthly thereafter during treatment with FOTIVDA).                                                                                                                                                                                                                                                                                                                                                                                   |
| 5 Warnings and Precautions | 5.4 Cardiac Failure                                                                             | Moved this earlier (from 5.4 to <b>5.2</b> ), because it was the most common adverse event leading to death. Added “FOTIVDA has not been studied in patients with symptomatic cardiac failure within the preceding 6 months before FOTIVDA treatment initiation.”                                                                                                                                                                    |
| 5 Warnings and Precautions | 5.2 Arterial and Venous Thrombotic Events                                                       | Separated this into: 5.3 (Cardiac Ischemia and Arterial Thromboembolic Events) and 5.4 (Venous Thromboembolic Events) to reflect groupings with similar pathophysiology. Added “FOTIVDA has not been studied in patients who had an arterial thrombotic event, myocardial infarction, or unstable angina within the preceding 6 months before FOTIVDA treatment initiation.”                                                         |
| 5 Warnings and Precautions | 5.3 Hemorrhagic Events                                                                          | (5.5) Added “FOTIVDA has not been studied in patients with significant bleeding within the preceding 6 months before FOTIVDA treatment initiation.”                                                                                                                                                                                                                                                                                  |
| 5 Warnings and Precautions | 5.6 Proteinuria                                                                                 | (5.6) Added “Of the patients who developed proteinuria, 3/81 (3.7%) had acute kidney injury either concurrently or later during treatment” and “Discontinue FOTIVDA in patients who develop nephrotic syndrome.”                                                                                                                                                                                                                     |
| 5 Warnings and Precautions | 5.5 Thyroid Dysfunction                                                                         | (5.7) Added overall thyroid dysfunction event incidence (including hypothyroid, hyperthyroid, and unspecified events).                                                                                                                                                                                                                                                                                                               |
| 5 Warnings and Precautions | 5.7  (b) (4) | (5.8) Renamed this “Risk of Impaired Wound Healing” given the lack of wound healing complications reported in the clinical data.<br>Changed instruction to “Withhold FOTIVDA for at least 24 days prior to elective surgery” for consistency with OOD labeling practices of recommending drugs claiming VEGF antagonism be held for 5 half lives prior to scheduled surgery. Added “Do not administer for at least 2 weeks following |

|                            |                                                                                    |                                                                                                                                                                                                                                                                                                                                          |
|----------------------------|------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                            |                                                                                    | major surgery and until adequate wound healing,” also for consistency with OOD labeling practices.                                                                                                                                                                                                                                       |
| 5 Warnings and Precautions | 5.8 Reversible Posterior Leukoencephalopathy Syndrome (RPLS)                       | (5.9) Removed the sentence (b) (4)<br>[Redacted] When FDA inquired of details, the sponsor reported that there were no MRI-confirmed cases of RPLS.                                                                                                                                                                                      |
| 5 Warnings and Precautions | 5.9 Embryo-fetal Toxicity                                                          | (5.10) Simplified language and removed (b) (4)<br>[Redacted]                                                                                                                                                                                                                                                                             |
| 6.1                        | The events described in ... (5.0) were obtained from analysis of 1008 RCC patients | Described the pooled safety population in more detail, including dosing regimen, duration of exposure, and most common adverse events.                                                                                                                                                                                                   |
| 6.1                        | TIVO-3                                                                             | Added fatal and serious adverse reactions. Removed results for the control arm, incidences of each AE, and modified language overall for consistency with OOD labeling practices.                                                                                                                                                        |
| 6.1                        | Table 2. (b) (4)<br>[Redacted]                                                     | Changed title to “Adverse Reactions (≥ 15%) in Patients Who Received FOTIVDA in TIVO-3.” Reorganized rows for consistency with OOD labeling practices. Removed absolute numbers and decimals, leaving only percentages rounded to the nearest whole number. Added footnotes to define composite terms.                                   |
| 6.1                        | Table 3. Laboratory Abnormalities Occurring in ≥ 10%                               | Changed title to “Select Laboratory Abnormalities Occurring in (≥ 10%) That Worsened from Baseline in Patients with Advanced RCC Who Received FOTIVDA.” Added footnote: “The denominator used to calculate the rate varied from 139 to 171 based on the number of patients with a baseline value and at least one post-treatment value.” |
| 7 Drug Interaction         | 7.1 CYP3A4 Inhibitors                                                              | Deleted section due to lack of clinical implication.                                                                                                                                                                                                                                                                                     |
|                            | 7.3 Transporters                                                                   | Deleted section due to the lack of clinical data.                                                                                                                                                                                                                                                                                        |
| 8 Use in Specific          | 8.5                                                                                | Removed sentence (b) (4)<br>[Redacted]                                                                                                                                                                                                                                                                                                   |

NDA/BLA Multi-disciplinary Review and Evaluation {NDA 212904}  
 {FOTIVDA, tivozanib}

|                           |                                                                   |                                                                                                                                                                                                                                                               |
|---------------------------|-------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Populations               |                                                                   | (b) (4) Added proportion of ≥75-year-olds. Modified claim of “no difference” to be limited to “effectiveness.”                                                                                                                                                |
| 8.7 Hepatic Impairment    | (b) (4)                                                           | Changed to “The recommended dosage of FOTIVDA in patients with severe hepatic impairment has not been established.”                                                                                                                                           |
| 10 Overdose               |                                                                   | Added language to emphasize the risk of death and hypertensive crisis associated with overdose.                                                                                                                                                               |
| 12.2 Pharmacodynamics     |                                                                   | Added lack of relationships identified.                                                                                                                                                                                                                       |
| 12.3 Pharmacokinetics     | Range of exposure at steady state                                 | Revised to geometric mean and %CV.                                                                                                                                                                                                                            |
| 12.3 Pharmacokinetics     | Different clearance and half-life in female and male.             | Changed to mean values due to the lack of clinical significance.                                                                                                                                                                                              |
| 12.3 Metabolism           | CYP3A4 and CYP1A1 are capable of metabolizing tivozanib           | Changed to “Tivozanib is metabolized predominantly by CYP3A4.”, as CYP1A1 is mainly expressed in extrahepatic tissues, it is unlikely that this isoform is involved in generating the metabolites observed following incubations with human liver microsomes. |
| 12.3 Specific populations | Hepatic impairment, dose adjustment based on Child-Pugh criteria. | Revised dose adjustment in patients with hepatic impairment based on NCI-ODWG criteria according to PopPK analysis.                                                                                                                                           |
| 12.3 Specific populations | (b) (4)                                                           | Deleted, as no dose adjustment is needed in patients with renal impairment (CLcr 15-89 mL/min).                                                                                                                                                               |
| 14 Clinical Studies       |                                                                   | Added dosing regimens in description of trial. Removed the statement that there was no statistically significant difference between the arms in OS, as it was apparent in the table.                                                                          |
| 14 Clinical Studies       | Table 4. Efficacy Results                                         | Deleted (b) (4) subgroup analyses, due to the exploratory nature of these analyses.                                                                                                                                                                           |
| 14 Clinical Studies       | Figure 1. Kaplan-Meier Plot of PFS                                | Revised figure so that the number of patients at risk started from n=175 in both arms (instead of (b) (4) in                                                                                                                                                  |

|                                   |  |                                                                                                                                                                                             |
|-----------------------------------|--|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                   |  | tivozanib and sorafenib, respectively).                                                                                                                                                     |
| 17 Patient Counseling Information |  | Added a section for infertility. Added advice for male patients with female partners of reproductive potential to use contraception during treatment and for one month after the last dose. |

### **11.1 Patient Labeling**

A Patient Package Insert (PPI) is included with FOTIVDA labeling. Changes made to the proposed PPI were done for consistency with package insert. This included the order of the serious side effects (for consistency with the Warnings & Precautions), adding instruction to “tell your healthcare provider about... medical conditions... including liver problems” in light of potential need for dose reduction, and adding specific symptoms associated with high blood pressure for which patients should monitor.

See the FDA OPDP/DMPP Review filed under this NDA for complete details.

## **12 Risk Evaluation and Mitigation Strategies (REMS)**

---

The Division of Risk Management and review team agreed that a REMS is not necessary to ensure the benefits outweigh the risks of tivozanib. This decision was made after considering several factors: the risks associated with tivozanib are well-described in Sections 5 and 6 of labeling, the life-threatening nature of the disease of relapsed/refractory advanced RCC, the limited treatment options available, and the clinically meaningful efficacy results seen in TIVO-3.

## **13 Postmarketing Requirements and Commitment**

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There are no postmarketing requirements or commitments for this application.

#### 14 Division Director (DHOT)

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X

\_\_\_\_\_  
John Leighton, PhD

#### 15 Division Director (OCP)

---

X

Nam A. Rahman -S

Digitally signed by Nam A. Rahman -S  
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA,  
ou=People, cn=Nam A. Rahman -S,  
0.9.2342.19200300.100.1.1=1300072597  
Date: 2021.03.10 10:11:36 -05'00'

#### 16 Division Director (OB) Comments

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X

#### 17 Division Director (Clinical) Comments

---

X

\_\_\_\_\_  
Laleh Amiri-Kordestani, MD

## **18 Office Director (or designated signatory authority) Comments**

*This application was reviewed by the Oncology Center of Excellence (OCE) per the OCE Intercenter Agreement. My signature below represents an approval recommendation for the clinical portion of this application under the OCE.*

X

## 19 Appendices

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### 19.1 References

1. Siegel RL, Miller KD, Fuchs HE, Jemal A. Cancer Statistics, 2021. CA: A Cancer Journal for Clinicians 2021; 71: 7-33.
2. Institute NC. Cancer Stat Facts: Kidney and Renal Pelvis Cancer. In. <https://seer.cancer.gov/statfacts/html/kidrp.html>: 2020.
3. Institute NC. Clear Cell Renal Cell Carcinoma. In. <https://www.cancer.gov/pediatric-adult-rare-tumor/rare-tumors/rare-kidney-tumors/clear-cell-renal-cell-carcinoma>: 2020.
4. Kane RC, Farrell AT, Saber H et al. Sorafenib for the treatment of advanced renal cell carcinoma. Clin Cancer Res 2006; 12: 7271-7278.
5. Escudier B, Eisen T, Stadler WM et al. Sorafenib in Advanced Clear-Cell Renal-Cell Carcinoma. New England Journal of Medicine 2007; 356: 125-134.
6. Rock EP, Goodman V, Jiang JX et al. Food and Drug Administration drug approval summary: Sunitinib malate for the treatment of gastrointestinal stromal tumor and advanced renal cell carcinoma. Oncologist 2007; 12: 107-113.
7. FDA. US Prescribing Information. NDA 021938s009 sunitinib malate (February 2007). [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2009/021938s009lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2009/021938s009lbl.pdf). In.
8. FDA. MEDICAL REVIEW(S). NDA 022465: pazopanib. [https://www.accessdata.fda.gov/drugsatfda\\_docs/nda/2009/022465s000\\_MedR.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/nda/2009/022465s000_MedR.pdf). October 19, 2009. In.
9. Motzer RJ, Hutson TE, Cella D et al. Pazopanib versus Sunitinib in Metastatic Renal-Cell Carcinoma. New England Journal of Medicine 2013; 369: 722-731.
10. FDA. MEDICAL REVIEW(S). NDA 202324: axitinib. [https://www.accessdata.fda.gov/drugsatfda\\_docs/nda/2012/202324Orig1s000MedR.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/nda/2012/202324Orig1s000MedR.pdf). January 27, 2012. In.
11. FDA. US Prescribing Information. NDA 208692s002 cabozantinib (December 2019). [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2017/208692s002lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/208692s002lbl.pdf). In.
12. Motzer RJ, Hutson TE, Tomczak P et al. Overall survival and updated results for sunitinib compared with interferon alfa in patients with metastatic renal cell carcinoma. J Clin Oncol 2009; 27: 3584-3590.
13. Sternberg CN, Hawkins RE, Wagstaff J et al. A randomised, double-blind phase III study of pazopanib in patients with advanced and/or metastatic renal cell carcinoma: final overall survival results and safety update. Eur J Cancer 2013; 49: 1287-1296.
14. Hutson TE, Lesovoy V, Al-Shukri S et al. Axitinib versus sorafenib as first-line therapy in patients with metastatic renal-cell carcinoma: a randomised open-label phase 3 trial. The Lancet Oncology 2013; 14: 1287-1294.
15. Hutson TE, Al-Shukri S, Stus VP et al. Axitinib Versus Sorafenib in First-Line Metastatic Renal Cell Carcinoma: Overall Survival From a Randomized Phase III Trial. Clin Genitourin Cancer 2017; 15: 72-76.

16. FDA. Summary Minutes - ODAC 5.2.13. In. <https://wayback.archive-it.org/7993/20170404153302/https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/OncologicDrugsAdvisoryCommittee/UCM359160.pdf>: 2013.
17. Motzer RJ, Escudier B, Tomczak P et al. Axitinib versus sorafenib as second-line treatment for advanced renal cell carcinoma: overall survival analysis and updated results from a randomised phase 3 trial. *Lancet Oncol* 2013; 14: 552-562.
18. Choueiri TK, Escudier B, Powles T et al. Cabozantinib versus everolimus in advanced renal cell carcinoma (METEOR): final results from a randomised, open-label, phase 3 trial. *The Lancet Oncology* 2016; 17: 917-927.
19. Escudier B, Sharma P, McDermott DF et al. CheckMate 025 Randomized Phase 3 Study: Outcomes by Key Baseline Factors and Prior Therapy for Nivolumab Versus Everolimus in Advanced Renal Cell Carcinoma. *European Urology* 2017; 72: 962-971.
20. Escudier B, Eisen T, Stadler WM et al. Sorafenib for treatment of renal cell carcinoma: Final efficacy and safety results of the phase III treatment approaches in renal cancer global evaluation trial. *J Clin Oncol* 2009; 27: 3312-3318.
21. FDA. Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products: Draft Guidance for Industry. In. <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/demonstrating-substantial-evidence-effectiveness-human-drug-and-biological-products>: 2019.
22. Tlemsani C, Mir O, Boudou-Rouquette P et al. Posterior reversible encephalopathy syndrome induced by anti-VEGF agents. *Target Oncol* 2011; 6: 253-258.
23. Sims JN, Yedjou CG, Abugri D et al. Racial Disparities and Preventive Measures to Renal Cell Carcinoma. *International journal of environmental research and public health* 2018; 15: 1089.
24. Krishnan B, Rose TL, Kardos J et al. Intrinsic Genomic Differences Between African American and White Patients With Clear Cell Renal Cell Carcinoma. *JAMA Oncology* 2016; 2: 664-667.

## 19.2 Financial Disclosure

### Covered Clinical Study (Name and/or Number): TIVO-3

|                                                                                                                |                                         |                                                           |
|----------------------------------------------------------------------------------------------------------------|-----------------------------------------|-----------------------------------------------------------|
| Was a list of clinical investigators provided:                                                                 | Yes <input checked="" type="checkbox"/> | No <input type="checkbox"/> (Request list from Applicant) |
| Total number of investigators identified: <u>803</u>                                                           |                                         |                                                           |
| Number of investigators who are Sponsor employees (including both full-time and part-time employees): <u>0</u> |                                         |                                                           |
| Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>0</u>            |                                         |                                                           |

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |                                         |                                                                  |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------|------------------------------------------------------------------|
| If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)):<br>Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: <u>0</u><br>Significant payments of other sorts: <u>0</u><br>Proprietary interest in the product tested held by investigator: <u>0</u><br>Significant equity interest held by investigator in <u>0</u><br>Sponsor of covered study: <u>0</u> |                                         |                                                                  |
| Is an attachment provided with details of the disclosable financial interests/arrangements:                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | N/A                                     |                                                                  |
| Is a description of the steps taken to minimize potential bias provided:                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | Yes <input checked="" type="checkbox"/> | No <input type="checkbox"/> (Request information from Applicant) |
| Number of investigators with certification of due diligence (Form FDA 3454, box 3) <u>795</u>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |                                         |                                                                  |
| Is an attachment provided with the reason:                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | Yes <input checked="" type="checkbox"/> | No <input type="checkbox"/> (Request explanation from Applicant) |

### 19.3 Nonclinical Pharmacology/Toxicology

The nonclinical studies for tivozanib hydrochloride were reviewed on May 24, 2013 under NDA # 204408 (Applicant-owned) for the the treatment of patients with advanced renal cell carcinoma (RCC).

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

**PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION**

Application number: 204408  
Supporting document/s: 1  
Applicant's letter date: 9/27/2012  
CDER stamp date: 9/28/2012  
Product: tivozanib hydrochloride  
Indication: Treatment of advanced renal cell carcinoma  
Applicant: AVEO Pharmaceuticals INC  
75 Sidney St 4th Fl  
Cambridge, Massachusetts 02139  
United States  
Review Division: Division of Hematology Oncology Toxicology  
(Division of Oncology Products 1)  
Reviewer: Eias Zahalka, PhD, MBA  
Supervisor: Todd Palmby, PhD  
Division Director: John Leighton, PhD, DABT (DHOT-Acting)  
Robert Justice, MD, MS (DOP1)  
Project Manager: Kim Robertson

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NDA # 204408

Reviewer: Eias A. Zahalka, PhD, MBA

|     |                                                      |            |
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## 1 Executive Summary

### 1.1 Introduction

NDA 204408 for tivozanib was submitted to the U.S. Food and Drug Administration as a New Drug Application (NDA) for the indication of the treatment of patients with advanced renal cell carcinoma (RCC). Tivozanib is a new molecular entity kinase inhibitor, which inhibits multiple kinases including vascular endothelial growth factor receptor (VEGFR)-1, VEGFR-2, and VEGFR-3. The recommended maximum human dose is 1.5 mg taken orally once daily, on a schedule of 3 weeks-on treatment followed by 1 week-off. Nonclinical pharmacology, pharmacokinetic and toxicology studies have been submitted to support the approval of tivozanib for the proposed indication.

### 1.2 Brief Discussion of Nonclinical Findings

Tivozanib hydrochloride is an anticancer agent of the Vascular Endothelial Growth Factor Receptor (VEGFR) Tyrosine Kinase inhibitor class and is being developed for the treatment of advanced renal cell carcinoma. *In vitro* cellular kinase assays demonstrated that tivozanib is an inhibitor of VEGF receptors -1, -2, and -3 ( $IC_{50}$  0.107, 0.081, and 0.122 ng/mL, respectively) and other kinases such as c-Kit and PDGFR $\beta$  at higher  $IC_{50}$ 's (0.83 and 0.88 ng/ml, respectively). The  $IC_{50}$  of these kinases is well below the  $C_{min}$  value achieved in RCC patients (16 to 30.9 ng/mL) following repeat dosing at the recommended dose at 1.5 mg/day, suggesting continuous inhibition of these kinases throughout the treatment period.

*In vivo* pharmacodynamic studies in mice and rats bearing human or murine xenograft tumors demonstrated that tivozanib inhibited tumor growth at a dose of 0.2 mg/kg in rats, via inhibition of angiogenesis and vascular permeability. This dose is associated with a plasma levels of tivozanib in rodents ( $C_{max}$  of 70 - 108 ng/ml; AUC of 1640 ng\*hr/ml), which were within range of the  $C_{max}$  and AUC achieved in RCC patients following repeat dosing at the recommended dose of 1.5 mg/day ( $C_{max}$  was 67.5 - 94.3 ng/mL; AUC<sub>0-24</sub> was 1180 -1641 ng\*hr/mL).

The selection of animal models to be used in toxicology and safety pharmacology studies (rats and monkeys) was based on PK and/or metabolic profiles of tivozanib. The oral route was utilized in nonclinical studies as this is the intended clinical route of exposure. The tivozanib toxicokinetic profile following repeat oral administration was approximately linear in rats and monkeys, with  $C_{max}$  and AUC increasing in an approximately dose proportional manner. No gender differences were shown in the rat or monkey. Interspecies differences in the rate of absorption ( $T_{max}$ ) and elimination half-life ( $t_{1/2}$ ) were reported. The elimination  $t_{1/2}$  in rats (9-45 hours) was greater than that reported in monkeys (8-12 hours), but was considerably shorter than that reported for humans (4.5-5.1 days). To account for these differences, the dosing regimen in the nonclinical toxicology studies was daily as compared to the clinical regimen (once daily, 3 weeks on and 1week off). In *in vitro* distribution studies conducted using animal

or human plasma, it was shown that tivozanib bound to plasma proteins at > 97.6%, and protein binding was predominantly to albumin, with low binding to  $\alpha$ -1-acid glycoprotein. Tivozanib mainly partitioned into the plasma/serum component of blood. *In vivo* metabolism studies demonstrated that the parent compound (tivozanib) was the major component in serum and feces of rats and monkeys. Tivozanib appeared to be metabolized mainly by oxidation, demethylation and glucuronidation. All prominent human metabolites (M1 through M24) were present in both rat and monkey, with the exception of M11, which was unique to human hepatocytes (minor >0.5%), and M10, which was not observed in rat hepatocytes. M14 was present at >10% and was designated as a major metabolite in human, monkey and rat. Comparison of the metabolic profile of tivozanib in liver microsomes showed that monkey most closely resembled the human, followed by the rat. These data provided support for species selection. Excretion studies in rats and monkeys showed that tivozanib was mainly excreted in feces in both species, and through the bile in rats.

In safety pharmacology studies, no effects on respiration rate, tidal volume, neurobehavioral endpoints or physiological parameters were reported in rat studies. In single and repeat-dose cardiovascular studies in telemetered cynomolgus monkeys, a dose of 3 mg/kg (HED= 58 mg/day; 39-fold of the recommended human dose) resulted in increases in systolic, diastolic and mean arterial blood pressure. At doses  $\geq 1$  mg/kg/day in the monkey (HED=19.5 mg/day; 13-fold of the recommended human dose), decreases in heart rate, cardiac output, renal arterial blood flow and cardiac arterial blood flow were reported. A decrease in vascular relaxation response and decrease in sensitivity to acetylcholine were also reported at doses  $\geq 1$  mg/kg/day, which may have played a role in the reported hypertension response in monkeys.

Using the core battery of genetic toxicology studies recommended in ICH guidances, tivozanib was not shown to be mutagenic, aneugenic or clastogenic; however, tivozanib produced changes in chromosomal number (polyploidy, hyperdiploidy) at  $\geq 2$   $\mu$ g/mL (1.2-fold times the plasma level at recommended human dose).

In a male and female fertility study in rats, doses  $\geq 0.1$  mg/kg/day resulted in a decrease in animal mating (HED=0.97 mg/day; 0.65-fold of the recommended human dose) and doses  $\geq 0.3$  mg/kg/day produced infertility (HED=2.9 mg/day; 1.95-fold of the recommended human dose). In an embryo-fetal developmental study in rats, tivozanib was administered during the period of organogenesis. Tivozanib at doses  $\geq 0.03$  mg/kg/day (HED=0.29 mg/day; 0.19-fold of the recommended human dose) resulted in maternal toxicity, increases in early and late resorptions, an increase in fetal external malformations (body edema, short tail and kinked tail) and an increase in skeletal developmental delays. In an embryo-fetal developmental study in rabbits, tivozanib at 1 mg/kg/day (HED=19.5 mg/day; 13-fold of the recommended human dose) administered orally during the period of organogenesis resulted in fetal malformations including ventricular septal defects, constricted pulmonary artery vessels and distended aorta. No maternal toxicity was reported.

In repeat-dose general toxicology studies, the toxicity profiles of tivozanib in the rat and monkey showed some overlap. The predominant toxicities in both species were associated with the following systems/organs: adrenal gland, gastrointestinal system (stomach, duodenum, and pancreas), kidney, bone (femur and tibia), liver, brain, pituitary gland, heart, incisors and reproductive system (ovaries and uterus). Clinical pathology changes and body weight decreases were also reported in both species.

Oral administration of tivozanib to rats for 13 weeks resulted in mortalities and severe clinical observations (clinical signs typically associated with morbidity, malocclusion, missing teeth and white teeth) at doses  $\geq 0.1$  mg/kg/day (HED=0.97 mg/day; 0.65-fold of the recommended human dose). The observed dental toxicity correlated with microscopic findings in the incisors of the rats which may have contributed to the reported decreases in body weights and food consumption. The effect on incisors is unlikely to be relevant to targeted patient population (adults) due to the difference in incisor growth patterns in rats and humans. Clinical pathology changes were reported at doses  $\geq 0.03$  mg/kg/day (HED=0.29; 0.19-fold the recommended human dose) and included changes in hematology (increases in RBC and WBC parameters), clinical chemistry (increases in iron metabolism, liver parameters, LDH/creatinine, triglycerides and renal parameters and decrease in protein parameters) and urine parameters (increases in protein, urobilinogen, bilirubin and hyaline casts). At doses  $\geq 0.1$  mg/kg/day (HED=0.97; 0.65-fold the recommended human dose) the target organs with significant toxicity were the adrenal glands, kidney, bone-femur, liver/ bile duct, brain, pituitary, incisors, pancreas and duodenum. Less pronounced (lower incidence and/or severity) microscopic findings were reported in the heart, reproductive organs, bone marrow, adrenal medulla and stomach. Partial recovery of most effects was reported at doses  $\geq 0.1$  mg/kg/day, although renal effects were not recoverable at these doses. Toxicities at doses  $\geq 0.3$  mg/kg/day overlapped with those at the lower doses, but were more severe, occurred at a higher incidence and were for the most part not recoverable. NOAEL was considered to be 0.03 mg/kg/day (HED = 0.29 g/day; 0.2-fold of the recommended human dose) based on adverse microscopic findings.

Oral administration of tivozanib in rats for 26 weeks produced non-adverse decreases in body weights, abnormal whitening of the teeth and changes in hematology/clinical chemistry at 0.08 mg/kg/day. No test article-related findings were reported by the end of the treatment or the recovery periods. The NOAEL was established to be the highest dose tested, 0.08 mg/kg/day (HED = 0.78g/day; 0.5-fold of the recommended human dose). The doses assessed in this study were low, and given the lack of appreciable toxicity, were considered insufficient to enable an adequate determination of dose-response relationships.

Oral administration of tivozanib in monkeys for 13 weeks produced microscopic findings in the brain and adrenal cortex at doses  $\geq 0.1$  mg/kg/day (HED=1.9 mg/day; 1.3-fold of the recommended human dose). At doses  $\geq 0.3$  mg/kg/day (HED=5.8 mg/day; 3.9-fold of the recommended human dose), adverse clinical signs, decrease in body weight and changes in hematology (increases in RBC, decreases and in WBC parameters), clinical and urine chemistry parameters (increases in CK, SELA- $\alpha$  &  $\beta$ , iron, phospholipids; decreases in ALP, SDH, total bile

acid, amylase, UIBC, U LDH and U creatinine) were reported. The predominant test article-related microscopic findings evident at doses  $\geq 0.3$  mg/kg/day included bone (femur and tibia), gastric system (stomach, duodenum and pancreas), reproductive system (ovary and corpora lutea) and lymphoid organs (lymphoid depletion of thymus, lymph nodes and spleen. The majority of the findings were recoverable after a 2- or 5-week recovery period. The NOAEL was established to be 0.1 mg/kg/day (1.3-fold of the recommended human dose).

In a 39-week oral toxicity study in monkeys, the highest dose tested 0.1 mg/kg/day (HED=1.95 g/day; 1.3-fold of the recommended human dose) was well tolerated and considered to the established NOAEL. As with the 26-week rat study, the doses assessed in the 39-week monkey study were low, and given the lack of appreciable toxicity, were considered insufficient to enable an adequate determination of dose-response relationships.

Ocular and cutaneous phototoxicity studies with tivozanib in rats did not show skin or ocular phototoxicity.

### 1.3 Recommendations

#### 1.3.1 Approvability

There are no non-clinical findings that would preclude the approval of tivozanib for the proposed indication.

#### 1.3.2 Additional Non Clinical Recommendations

None

## 2 Drug Information

### 2.1 Drug: Tivozanib hydrochloride

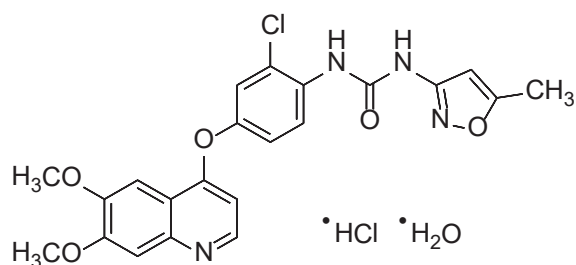
*Generic Name:* tivozanib hydrochloride

*Code Name:* AV-951, KRN951

*Chemical Name:* 1-{2-chloro-4-[(6,7-dimethoxyquinolin-4-yl)oxy]phenyl}-3-(5-methylisoxazol-3-yl)urea hydrochloride hydrate

*Molecular Formula/Molecular Weight:* C<sub>22</sub>H<sub>19</sub>ClN<sub>4</sub>O<sub>5</sub> • HCl • H<sub>2</sub>O / 509.34.

*Structure*



*Pharmacologic Class:* kinase inhibitor

## 2.2 Relevant INDs, NDAs, BLAs and DMFs: IND (b) (4)

### 2.3 Drug Formulation

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. Two strengths of the drug product in size 4 hard gelatin capsule will be available: 1.0 mg and 1.5 mg.

**Table 1: Composition of the Tivozanib Hydrochloride 1.0 mg and 1.5 mg Capsules**

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

<sup>1</sup> USP-NF: USP = United States Pharmacopeia; NF = National Formulary

<sup>2</sup> Each capsule contains 1.0 mg tivozanib hydrochloride equivalent to 0.89 mg tivozanib (free base).

<sup>3</sup> Each capsule contains 1.5 mg tivozanib hydrochloride equivalent to 1.34 mg tivozanib (free base).

<sup>4</sup> (b) (4)

(excerpted from Applicant's report)

## 2.4 Comments on Novel Excipients

There are no novel excipients.

## 2.5 Comments on Impurities/Degradants of Concern

*Impurities above the ICH qualification threshold:*

There are two impurities above the ICH qualification threshold: (b) (4) in Drug Substance and (b) (4) in Drug Product). (b) (4) has a genotoxic concern (Ames positive). The impurity levels as specified below are considered acceptable from the pharmacology/toxicology perspective.

In addition, (b) (4) is also a degradant in both the drug substance and the drug product (NMT (b) (4) %). The degradant level is considered qualified based on the qualification criteria established by the ICH Q3B(R2) guideline.



**Reviewer Comments:**

- The maximum daily dose of tivozanib in the clinic is 1.5 mg.
- The specification limit for (b) (4) is NMT (b) (4) %, and for (b) (4) is NMT (b) (4) %. In the drug product these limits translate to a maximum daily dose of (b) (4) µg of (b) (4) and (b) (4) µg of (b) (4).
- Lot CDM-001 had the highest impurity levels of (b) (4) used for nonclinical studies. As such, it will be used to qualify these impurities.
- Lot CDM-001 was used in a GLP 13-Week gavage toxicity and toxicokinetic study with a 5-Week recovery period with KRN951 in cynomolgus monkeys (Study # 6691-159).
- In study # 6691-159, the dose of 1.0 mg/kg/day (HED 19.5 mg/day) was considered the highest non-severely toxic dose (HNSTD) in monkey.

- At a dose of 1.0 mg/kg/day (HED 19.5 mg/day), the daily dose of impurities a monkey received was [REDACTED] <sup>(b) (4)</sup>. These levels of impurities per day in the nonclinical study are higher than the level of impurities per day that would be administered at the clinical dose.



*Conclusion:* The daily impurity levels of [REDACTED] <sup>(b) (4)</sup> (a genotoxic impurity) in the nonclinical studies exceed the daily impurity levels at the recommended clinical doses. Given that no severe toxicity was reported at these impurity levels in nonclinical studies, the impurities levels as specified are considered qualified by the nonclinical data. In addition, the maximum daily dose of the genotoxic impurity [REDACTED] <sup>(b) (4)</sup> µg/day in patients receiving 1.5 mg/day of tivozanib. As levels of genotoxic impurities in anticancer pharmaceuticals may exceed the threshold of toxicologic concern based on lifetime daily exposures as per ICH S9 recommendations, the specification for [REDACTED] <sup>(b) (4)</sup> in the tivozanib DP is acceptable based on the indicated patient population.

## 2.6 Proposed Clinical Population and Dosing Regimen

The proposed tivozanib hydrochloride regimen for the treatment of patients with advanced RCC is 1.5 mg daily for 3 weeks (21 days) followed by a 1-week (7 days) rest period. When dose reduction is needed, the dose may be reduced to 1.0 mg daily for 3 weeks followed by a 1-week rest period.

## 2.7 Regulatory Background

Original IND [REDACTED] <sup>(b) (4)</sup> was submitted to the FDA on April 30, 2007.

## 3 Studies Submitted

| Study #                             | Study Title                                                                                                                                                      | Reviewed |            |
|-------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------|------------|
|                                     |                                                                                                                                                                  | Full     | Summarized |
| <b>Pharmacology Studies-Primary</b> |                                                                                                                                                                  |          |            |
| KBC008                              | KinaseProfiler™: Overall Selectivity of Inhibition Against Multiple Recombinant Kinases                                                                          |          | X          |
| KBC009                              | KinaseProfiler™: Overall Selectivity of Inhibition Against Multiple Recombinant Kinases                                                                          |          | X          |
| KBC010                              | KinaseProfiler™: Overall Selectivity of Inhibition Against Multiple Recombinant Kinases                                                                          |          | X          |
| 1172                                | IC <sub>50</sub> profiling of 2 compounds using 26 protein kinases                                                                                               |          | X          |
| 951-09                              | Evaluation of Inhibitory Activity of KRN951 on VEGFR-2 Receptor Tyrosine Kinase                                                                                  | X        |            |
| 951-03                              | Evaluation of Inhibitory Activity of KRN951 on VEGFR-1 Receptor Tyrosine Kinase                                                                                  | X        |            |
| 951-41                              | Assessment of VEGFR-3 Receptor Tyrosine Kinase Inhibiting Effect of KRN951                                                                                       | X        |            |
| 951-16                              | Evaluation of Inhibitory Activity of KRN951 on c-Kit Receptor Tyrosine Kinase                                                                                    | X        |            |
| 951-14                              | Evaluation of Inhibitory Activity of KRN951 on PDGFR β Receptor Tyrosine Kinase                                                                                  | X        |            |
| 951-33                              | Evaluation of Inhibitory Activity of KRN951 on FGFR-1 Receptor Tyrosine Kinase                                                                                   | X        |            |
| 951-27                              | Evaluation of Inhibitory Activity of KRN951 on Flt3 Receptor Tyrosine Kinase                                                                                     | X        |            |
| 951-23                              | Evaluation of Inhibitory Activity of KRN951 on c-Met Receptor Tyrosine Kinase                                                                                    | X        |            |
| 951-34                              | Evaluation of Inhibitory Activity of KRN951 on EGFR Receptor Tyrosine Kinase                                                                                     | X        |            |
| 951-36                              | Evaluation of Inhibitory Activity of KRN951 on IGF-I R Receptor Tyrosine Kinase                                                                                  | X        |            |
| 951-04                              | Evaluation of KRN951 Vascular Endothelial Cell Antiproliferative Activity                                                                                        | X        |            |
| 951-28                              | Study of Cell Growth Inhibition of KRN951 on Human Tumor Cells (WST-1 Assay)                                                                                     | X        |            |
| AV951-08195                         | Tivozanib (AV-951) Antitumor Activity as Monotherapy or in Combination with Rapamycin in ICR/SCID Mice Bearing Human Renal Cell Carcinoma 786-O Xenograft Tumors | X        |            |
| AV951-08048                         | AV-951: Antitumor Activity of AV-951 in a Murine Lung Kras Tumor Xenograft Model                                                                                 | X        |            |
| 951-24                              | Antitumor Efficacy of KRN951 on Nude Mouse Subcutaneously-Implanted Human Lung Carcinoma A549                                                                    | X        |            |

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|                               |                                                                                                                                                            |   |  |
|-------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------|---|--|
| 951-08                        | Antitumor Efficacy of KRN951 on Nude Mouse Subcutaneously-Implanted Human Lung Cancer Calu6                                                                | X |  |
| 951-25                        | Antitumor Efficacy of KRN951 on Nude Mouse Subcutaneously-Implanted Human Colon Cancer HT29                                                                | X |  |
| 951-06                        | Antitumor Efficacy of KRN951 on Nude Mouse Subcutaneously-Implanted Human Colon Cancer SW620                                                               | X |  |
| 951-05                        | Antitumor Efficacy of KRN951 on Nude Mouse Subcutaneously-Implanted Human Colon Cancer COLO205                                                             | X |  |
| 951-11                        | Antitumor Efficacy of KRN951 on Nude Mouse Subcutaneously-Implanted Human Prostate Carcinoma DU145                                                         | X |  |
| 951-13                        | Antitumor Efficacy of KRN951 on Nude Mouse Subcutaneously-Implanted Human Prostate Carcinoma PC-3                                                          | X |  |
| 951-12                        | Antitumor Efficacy of KRN951 on Nude Mouse Subcutaneously-Implanted Human Prostate Carcinoma LNCap                                                         | X |  |
| PRT/02149-1                   | Antitumor Activity of KRN951 Administered Per Os in Nude Rats Bearing Subcutaneous Human Tumors                                                            | X |  |
| 951-31                        | Antitumor Efficacy of KRN951 on Nude Rat Subcutaneously-Implanted Human Lung Carcinoma A549                                                                | X |  |
| AV951-08008                   | AV-951: AV-951 PD Analysis in Nude Mice Bearing Murine Breast HER2 Xenograft Tumors After Continuous Daily Oral Dosing of 5 mg/kg or 20 mg/kg              | X |  |
| 951-38                        | Angiogenesis and Vascular Permeability Suppression Activity of KRN951 on Nude Rat Subcutaneously-Implanted Human Lung Carcinoma A549                       | X |  |
| AV951-08046                   | AV-951: Antitumor Activity of AV-951 in Combination with Rapamycin in an Acquired AV-951-Resistant Murine Breast HER2 Tumor Xenograft Model                | X |  |
| AV951-08011R                  | AV-951: Effect of AV-951 in Combination with Rapamycin on Tumor Growth In Vivo: Genetically Engineered Breast HER2 Tumors                                  | X |  |
| 951-39                        | Anti-Tumor Effect of KRN951 Long –Term Dosing and Intermittent Dosing of Nude Mice with Subcutaneous Implanted Human Prostate Carcinoma (Cell Line DU 145) | X |  |
| <b>Pharmacokinetic / ADME</b> |                                                                                                                                                            |   |  |

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|             |                                                                                                                                                                                                                                                                                                                     |   |              |
|-------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---|--------------|
| KBLL_AA03   | Partial validation of a high performance liquid chromatographic-mass spectrometric method for the analysis of KRN951 in rabbit serum                                                                                                                                                                                |   | Not Reviewed |
| PK0306      | Quantitative assay for KRN951 in rat serum using the LC-MS/MS method                                                                                                                                                                                                                                                |   | Not Reviewed |
| KBLL-AA02   | Validation of a High Performance Liquid Chromatographic-Mass Spectrometric Method for the Analysis of KRN951 in Monkey Serum                                                                                                                                                                                        |   | Not Reviewed |
| 1458-009    | Validation of the Analytical Method: Method of Analysis for the Determination of AV-951 in Monkey Serum by LC/MS/MS                                                                                                                                                                                                 |   | Not Reviewed |
| DRZZ1016    | Study DRZZ1016 - Analytical Method Reports                                                                                                                                                                                                                                                                          |   | Not Reviewed |
| 1458-007    | Full Validation of an LC-MS/MS Assay For AV-951 in Rat Serum                                                                                                                                                                                                                                                        |   | Not Reviewed |
| SEL/1719    | Analytical Method Reports                                                                                                                                                                                                                                                                                           |   | Not Reviewed |
| DRZZ1003    | Validation of an Analytical Procedure for the Determination of KRN951 in Primate Serum and Partial Validations in Rat and Mouse Serum using Protein Precipitation with Tandem Mass Spectrometric Detection - The Validation will also include 1-Month Stability for KRN951 in Primate, Rat and Mouse Serum at -20°C |   | Not Reviewed |
| DRZZ1007    | Determination of the Stability of KRN951 in Primate and Mouse Serum Over a Storage Period of 6 Months at -20°C and Rat Serum Over a Storage Period of 7 Months at -20°C                                                                                                                                             |   | Not Reviewed |
| AV951-08030 | <i>AV-951 Serum Pharmacokinetics in Female NCr nu/nu Mice After a Single Oral Dose of 0.5 mg/kg, 1 mg/kg or 2 mg/kg</i>                                                                                                                                                                                             |   | Not Reviewed |
| AV951-08028 | <i>Tivozanib: Tivozanib Plasma Pharmacokinetics in Female NCr nu/nu Mice After a Single Oral Dose of 5 mg/kg or 20 mg/kg</i>                                                                                                                                                                                        |   | X            |
| PK0401      | <i>Pharmacokinetic Study of KRN951 - Serum Concentration-Time Profiles in Rats After Single Dosing</i>                                                                                                                                                                                                              |   | Not Reviewed |
| PKP0227     | KRN951 Serum Kinetics Experiment in Nude Rats                                                                                                                                                                                                                                                                       | X |              |
| DRZZ1040    | Whole Body Phosphor Imaging in Male and Female Rats Following a Single Oral Administration of [14C] KRN951                                                                                                                                                                                                          | X |              |
| DRZZ1039    | Determination of the In Vitro Binding of [14C] KRN951 to Plasma Proteins in Rat, Monkey and Human                                                                                                                                                                                                                   | X |              |
| 8236152     | Distribution - The In Vitro Protein Binding of 14C-Tivozanib to Human Plasma and Serum, Albumin and Human alpha1-Acid Glycoprotein, Protein Binding Interactions, and Human Blood to Plasma Partitioning                                                                                                            | X |              |
| 8255110     | Metabolism of 14C-Tivozanib Following Oral Administration to Rats                                                                                                                                                                                                                                                   | X |              |

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|                            |                                                                                                                                                                            |   |   |
|----------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---|---|
| 8255111                    | Metabolism of 14C-Tivozanib Following Oral Administration to Monkeys                                                                                                       | X |   |
| DRZZ1027                   | Comparison of the Metabolic Profile of KRN951 in Human, Primate, Dog and Rat Liver Microsomes and in Supersomes™ Over Expressing Individual Human Cytochrome P450 Isoforms | X |   |
| 8201725                    | In Vitro Metabolism of AV-951 in Rat, Monkey, and Human Primary Hepatocytes, and the In Vitro Metabolism of 14C-AV-951 in Human Primary Hepatocytes                        | X |   |
| 8133-100                   | Metabolism - In Vitro Metabolism of AV-951 in Human Hepatic Microsomes                                                                                                     | X |   |
| 8242516                    | Metabolism - Identification of Human UGT Isoenzymes Involved in the Metabolism of 14C Tivozanib and Associated Inhibitory Interacti                                        |   | X |
| PK0501                     | Metabolism - In Vitro Drug-Drug Interaction Study of AV951 – Determination of IC50 of AV951 Against CYP Probe Substrates                                                   | X |   |
| AV951-08274                | Metabolism - In Vitro Biotransformation of Tivozanib (AV-951)                                                                                                              |   | X |
| 8231061                    | Metabolism - Evaluation of AV951 on Cytochrome P450 Induction using Primary Cultures of Human Hepatocytes                                                                  |   | X |
| 8231062                    | Metabolism - Determination of the Apparent Permeability of <sup>14</sup> C-AV-951 through Caco-2 Monolayers and Evaluation as a P-gp Substrate and Inhibitor               |   | X |
| DRZZ1028                   | The Disposition of Total Radioactivity in the Rat Following Single Oral and Single Intravenous Administration of [14C] KRN951                                              | X |   |
| PK0403                     | Pharmacokinetic Study of AV951 – Biliary Excretion of [14C] AV951 in Rats                                                                                                  | X |   |
| <b>Safety Pharmacology</b> |                                                                                                                                                                            |   |   |
| DRZZ1020                   | Effect of KRN951 on HERG Tail Current Recorded from Stably Transfected HEK293 Cells                                                                                        | X |   |
| DRZZ1019                   | Cardiovascular Effects of KRN951 in Conscious, Telemetered Cynomolgus Monkeys                                                                                              | X |   |
| 4655                       | KRN951 Multiple Oral Dosing in Crab Eating Monkeys (Cynomolgus Monkey) Toxicity Study                                                                                      | X |   |
| DRZZ1017                   | Effects of KRN951 in the Irwin Test in Rats                                                                                                                                | X |   |
| DRZZ1018                   | Effects of KRN951 on Respiration Rate and Tidal Volume in Rats                                                                                                             | X |   |
| <b>Toxicology Studies</b>  |                                                                                                                                                                            |   |   |
| RZZ1011                    | Acute Oral Toxicity Study in the Mouse with KRN951 Including Toxicokinetic Sampling.                                                                                       |   | X |
| RZZ1010                    | Acute Intravenous Toxicity Study in the Mouse with KRN951 Including Toxicokinetic Sampling.                                                                                |   | X |

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|                                |                                                                                                                                                |          |                         |
|--------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------|----------|-------------------------|
| RZZ1009                        | Acute Oral Toxicity Study in the Rat with KRN951 Including Toxicokinetic Sampling (THIS IS A SINGLE DOSE WITH 14 DAY OBSERVATION STUDY).       |          | <b>X</b>                |
| RZZ1008                        | Acute Intravenous Toxicity Study in the Rat with KRN951 Including Toxicokinetic Sampling (THIS IS A SINGL DOSE WITH 14 DAY OBSERVATION STUDY). |          | <b>X</b>                |
| RZZ1012                        | Oral 7 Day Dose Range Finding Study with KRN951 in the Rat with Toxicokinetic Evaluation.                                                      |          | Not Reviewed            |
| RZZ1013                        | Four Week Oral Repeat Dose Toxicity Study with a 4 Week Recovery Period with KRN951 in the Rat.                                                |          | Reviewed during the IND |
| 6691-158                       | 13-Week Oral Gavage Toxicity and Toxicokinetic Study with a 5-Week Recovery Period with KRN951 in Rats.                                        | <b>X</b> |                         |
| 1458-005                       | AV-951: A 26-week oral toxicity study in rats with a 6-week recovery period.                                                                   | <b>X</b> |                         |
| RZZ1014                        | Oral (Gavage) Maximum Tolerated Dose (MTD) and 14 Day Repeat Dose Study with KRN951 in the Cynomolgus Monkey with Toxicokinetic Evaluation.    |          | Not Reviewed            |
| RZZ1015                        | Four Week Oral (Gavage) Repeat Dose Toxicity Study with a 4 Week Recovery Period with KRN951 in the Cynomolgus Monkey                          |          | Reviewed during the IND |
| 6691- 159                      | 13-Week Gavage Toxicity and Toxicokinetic Study with a 5-Week Recovery Period with KRN951 in Cynomolgus Monkeys.                               | <b>X</b> |                         |
| 1458-006                       | AV-951: a 39-week oral toxicity study in cynomolgus monkeys with a 6-week recovery period.                                                     | <b>X</b> |                         |
| <b>Reproductive Toxicology</b> |                                                                                                                                                |          |                         |
| 311-007p                       | Oral (Gavage) Dosage-Range Fertility and General Reproduction Toxicity Study of KRN951 in Rats.                                                | <b>X</b> |                         |
| 311-007                        | Oral (gavage) fertility (m+f) and general reproduction toxicity study of KRN951 in rats.                                                       | <b>X</b> |                         |
| 311-005p                       | Oral (Gavage) dosage-range developmental toxicity study of KRN951 in rats.                                                                     | <b>X</b> |                         |
| 311-005                        | Oral (Gavage) developmental toxicity study of KRN951 in rats.                                                                                  | <b>X</b> |                         |
| 311-006p                       | Oral (Stomach Tube) Dosage-Range Developmental Toxicity Study of KRN951 in Rabbits.                                                            | <b>X</b> |                         |
| 311-006                        | Oral (stomach tube) developmental toxicity study of KRN951 in rabbits, including a toxicokinetic evaluation.                                   | <b>X</b> |                         |

| <b>Genetic Toxicology</b>            |                                                                                                                                 |   |  |
|--------------------------------------|---------------------------------------------------------------------------------------------------------------------------------|---|--|
| RCK0001                              | Bacterial Reverse Mutation Test (Ames)                                                                                          | X |  |
| RCK0002                              | <i>In Vitro</i> Mammalian Cell Cytogenetic Test: Chinese Hamster Ovary Cells.                                                   | X |  |
| RCK0003                              | Mouse Micronucleus Test.                                                                                                        | X |  |
| <b>Genetic Toxicology-Impurities</b> |                                                                                                                                 |   |  |
| ZNA39692.001                         | AV951-08275: The Analysis of Basic Structure Activity Relationships (SAR) for Tivozanib Related Structures using Derek          | X |  |
| 8240761                              | Reverse mutation in five histidine-requiring strains of <i>Salmonella typhimurium</i>                                           | X |  |
| 8242172                              | Reverse mutation in five histidine-requiring strains of <i>Salmonella typhimurium</i>                                           | X |  |
| 790081                               | (b) (4) Testing for Mutagenic Activity with <i>Salmonella typhimurium</i> TA 1535, TA 100, TA 1537, TA 98 and TA 102 (OECD 471) | X |  |
| 790102                               | (b) (4) Testing for Mutagenic Activity with <i>Salmonella typhimurium</i> TA 1535, TA 100, TA 1537, TA 98 and TA 102 (OECD 471) | X |  |
| 790118                               | (b) (4) Testing for Mutagenic Activity with <i>Salmonella typhimurium</i> TA 1535, TA 100, TA 1537, TA 98 and TA 102 (OECD 471) | X |  |
| 790123                               | (b) (4) Testing for Mutagenic Activity with <i>Salmonella typhimurium</i> TA 1535, TA 100, TA 1537, TA 98 and TA 102 (OECD 471) | X |  |
| 790139                               | (b) (4) Testing for Mutagenic Activity with <i>Salmonella typhimurium</i> TA 1535, TA 100, TA 1537, TA 98 and TA 102 (OECD 471) | X |  |
| 790097                               | (b) (4) Testing for Mutagenic Activity with <i>Salmonella typhimurium</i> TA 1535, TA 100, TA 1537, TA 98 and TA 102 (OECD 471) | X |  |
| 790144                               | (b) (4) Testing for Mutagenic Activity with <i>Salmonella typhimurium</i> TA 1535, TA 100, TA 1537, TA 98 and TA 102 (OECD 471) | X |  |
| 790165                               | (b) (4) Testing for Mutagenic Activity with <i>Salmonella typhimurium</i> TA 1535, TA 100, TA 1537, TA 98 and TA 102 (OECD 471) | X |  |
| 790338                               | Testing for Mutagenic Activity with <i>Salmonella typhimurium</i> TA 1535, TA 100, TA 1537, TA 98 and TA 102 (OECD 471)         | X |  |

|                                 |                                                                                                                                         |   |              |
|---------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------|---|--------------|
| 790778                          | (b) (4) Testing for Mutagenic Activity with <i>Salmonella typhimurium</i> TA 1535, TA 100, TA 1537, TA 98 and TA 102 (OECD 471)         | X |              |
| <b>Other Toxicology studies</b> |                                                                                                                                         |   |              |
| H1518B                          | Effects on KRN951 on the Liver.                                                                                                         |   | Not Reviewed |
| H1549B                          | Analysis over time of metabonomics of KRN951 in rats.                                                                                   |   | Not Reviewed |
| H1625B                          | KRN951 10-Day Repeated Administration Toxicity Testing in Rats.                                                                         |   | Not Reviewed |
| 311-003                         | Ultraviolet radiation and visible light absorption (290 to 700 nm) profile study of KRN951                                              |   | X            |
| 311-004                         | Single-dosage phototoxicity study to determine the effects of oral (gavage) administration of KRN951 on eyes and skin in pigmented rats |   | X            |

## 4 Pharmacology

### 4.1 Primary Pharmacology

#### 4.1.1 Mechanism of action:

Tivozanib hydrochloride (referred to as KRN951, AV-951 or tivozanib) is an anticancer agent of the vascular endothelial growth factor receptor (VEGFR) Tyrosine Kinase inhibitor class which is being developed for the treatment of advanced renal cell carcinoma (RCC). *In vitro* biochemical and cellular based kinase assays demonstrated that tivozanib inhibits phosphorylation of vascular endothelial growth factor receptors (VEGFR) -1, -2 and -3 (IC<sub>50</sub> of 0.21, 0.16 and 0.24 nM, respectively), and inhibited C-kit and PDGFR β at higher concentrations (IC<sub>50</sub> of 1.63 and 1.72 nM, respectively). Other kinases were inhibited at IC<sub>50</sub> ≥ 229 nmol/L. Tivozanib in *in vivo* tumor model studies was shown to inhibit angiogenesis and vascular permeability in tumor tissues at doses of 0.2 mg/kg/day and 5 mg/kg/day in rats and mice, respectively. Tivozanib administration resulted in anti-tumor effects, including tumor necrosis, growth inhibition, hypoxia and decreased angiogenesis.

#### Overall summary:

*In vitro* studies demonstrated that tivozanib is an inhibitor of VEGFRs and other kinases (e.g., c-Kit and PDGFR β).

- Tivozanib was tested in an *in vitro* biochemical kinase assay using a panel of 26 recombinant kinases at concentrations ranging from 0.3 nM to 10 μM. Tivozanib inhibited the phosphorylation of VEGF receptors -1, -2, and -3, with IC<sub>50</sub> values of 30, 6, and 15 nM, respectively.

- Tivozanib at concentrations ranging from 0.1 to 100 nM, was screened in an *in vitro* biochemical kinase assay using a panel of 129 recombinant kinases. At concentration of 100 nM, 39 kinases were inhibited by  $\geq 50\%$ . VEGFR-1, -2, and -3 were inhibited, with 18%, 0, and 3% activity remaining relative to control, respectively.
- In an *in vitro* cellular kinase assay performed in cultured human umbilical vein endothelial cells (HUVEC), tivozanib inhibited the activation of VEGF pathway by blocking the phosphorylation of VEGFR-1 ( $IC_{50}$  of 0.21 nmol/L) and VEGFR-2 ( $IC_{50}$  of 0.16 nmol/L). Tivozanib also inhibited VEGFR-3 autophosphorylation via VEGF with  $IC_{50}$  of 0.24 nmol/L in the murine 3T3 cell line. Activity against other kinases was also reported, as tivozanib inhibited c-Kit and PDGFR  $\beta$  with  $IC_{50}$ 's of 1.63 nmol/L and 1.72 nmol/L, respectively. In other cell types, kinases including FGFR-1, Flt3, c-Met, EGFR and IGF-I R were inhibited with  $IC_{50}$  values ( $\geq 229$  nmol/L)  $\sim 1000X$  higher than values reported for VEGFRs.

In *in vivo* tumor xenograft model studies in mice and rats, it was demonstrated that tivozanib inhibited tumor growth of various tumor cell types via inhibition of angiogenesis and vascular permeability.

- The inhibitory activity of tivozanib on tumor growth through VEGFR inhibition was supported by data from an *in vivo* study in which the inhibition of human tumor cell growth (A549, Calu-6, HT29, Colo205, SW620, DU145, LNCaP and PC-3) by tivozanib was evident, but at much higher concentrations ( $IC_{50} \geq 1$   $\mu\text{mol/L}$ ) relative to what was reported for VEGF-induced vascular endothelial cell growth ( $IC_{50}$  of 0.67 nmol/L). These data suggest that the antitumor activity of tivozanib on human tumors is a result of anti-angiogenic activity rather than direct growth suppression of cancer cells.
- Oral treatment with tivozanib at 5 and 20 mg/kg/day for 14 days resulted in tumor growth inhibition of a panel of 8 human cancer cell lines (lung, prostate, colon and renal) implanted in nude or ICR/SCID (renal model) mice. Tumor growth regression was reported in tivozanib-treated SCID mice xenografted with murine lung tumor cells and mice xenografted with human prostate carcinoma (DU145) tumor cells.
- Oral treatment for up to 14 consecutive days with tivozanib (0.2 and 1 mg/kg/day) in nude rat xenograft models bearing 15 different human cancer cell lines (pancreas, kidney, lung, glioma, prostate, colon, breast, ovary and liver) resulted in inhibition of tumors in a dose-dependent manner. At 0.2 mg/kg/day, tumor growth inhibition (TGI) was evident in 11 out of 15 of the cell line models (TGI $\geq 50\%$ ); and at 1 mg/kg/day in 14 out of 15 models (TGI  $\geq 86\%$ ).
- In a human lung carcinoma (A549) nude rat model treated orally for 7 days at 1 mg/kg/day and immunostained with a vascular endothelial cell-specific marker, intratumor angiogenesis inhibition was evident by the reduction in intratumor vascular endothelial cells. In another study using a similar rat model, the quantity of Evans blue dye (identifies vasculature permeability) in tumor tissues was evaluated. It was demonstrated that tivozanib at 0.2 and 1 mg/kg/day, inhibited angiogenesis and vascular permeability.
- In a repeat-dose study (up to 5 days) in nude mice bearing murine breast HER2 xenograft tumors, tivozanib at 5 and 20 mg/kg/day was reported to result in a dose-dependent

decrease in viable tumor area, reduction in total number of proliferating cells, decrease in vessel cross-section area, decrease in microvascular density and increase in tumor hypoxia as measured by HIF1- $\alpha$  protein.

- A combined treatment of tivozanib and rapamycin in mice bearing human BH504R3 or BH469 murine breast HER2 tumors in a xenograft tumor model resulted in an inhibition of tumor cell proliferation and with a decrease in viable tumor areas.

These studies are presented below:

|                                                                   |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
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| <p><b>Study #:<br/>1172</b></p>                                   | <p><b>Title:</b> IC<sub>50</sub> profiling of 2 compounds using 26 protein kinases<br/> <b>GLP:</b> No<br/> <b>Objectives:</b> The IC<sub>50</sub> profile of KRN-633 and KRN-951 (tivozanib), was determined using 26 protein kinases. IC<sub>50</sub> values were measured by testing 10 concentrations of each compound. <i>Only results from KRN-951 will be discussed in this review.</i></p> <p><b>Methods:</b></p> <ul style="list-style-type: none"> <li>• Protein kinases: EGF-R, EPHB4, IGF1-R, VEGF-R1, VEGF-R3, BRK, FGF-R1, FGF-R3, ABL1, ERBB4, FLT3, EPHB2, INS-R, JAK2, MET, MUSK, PDGFR-alpha, PDGFR-beta, KIT, WEE1, SRC, TIE2, VEGF-R2, ERBB2, FGF-R4 and FAK.</li> <li>• Tivozanib was tested over a concentration range of 0.3 nM to 10 <math>\mu</math>M.</li> </ul> <p><b>Results:</b><br/>                 Tivozanib inhibited the kinases activity in decreasing order: VEGFR-2 (IC<sub>50</sub> = 6 nM), VEGFR-3 (IC<sub>50</sub> = 15 nM), Eph-B2 (IC<sub>50</sub> = 24 nM), VEGFR-1 (IC<sub>50</sub> = 30 nM), PDGFR-<math>\alpha</math> (IC<sub>50</sub> = 40 nM), PDGFR-<math>\beta</math> (IC<sub>50</sub> = 49 nM), BRK (IC<sub>50</sub> = 48 nM), Tie-2 (IC<sub>50</sub> = 78 nM), and c-Kit (IC<sub>50</sub> = 78 nM). Other kinases tested demonstrated IC<sub>50</sub> values &lt; 475 nM (Eph-B4).</p> <p><b>Conclusion:</b><br/>                 The Applicant concluded that tivozanib inhibited the activity of all 3 VEGF receptors at low concentrations with IC<sub>50</sub> of 30, 6, and 15 nM for VEGFR-1 VEGFR-2, and VEGFR-3, respectively. Additionally, tivozanib inhibited several other kinases in these assays with IC<sub>50</sub> values ranging from 24 to 618 nM. The provided data supported this conclusion.</p> |
| <p><b>Study #:<br/>KBC008,<br/>KBC009,<br/>and<br/>KBC010</b></p> | <p>Three <i>in vitro</i> studies were designed to assess the selectivity of tivozanib for kinases. Tivozanib was screened against an expanded panel of 129 recombinant kinases <i>in vitro</i> at concentrations ranging from 0.1 to 100 nM to determine its inhibitory activity. At concentrations of 0.1 and 10 nM minimal inhibition was reported for any kinase. At a concentration of 10 nM, 12 kinases showed inhibition of <math>\geq</math> 50%. (JAK-3, c-Kit, CSF1R, BRK, and Abl-1). At a concentration of 100 nM, 39 kinases (including 4 mutations of mast/stem cell growth factor receptor [c-Kit] and 2 alleles of platelet-derived growth factor receptor-<math>\alpha</math> [PDGFR-<math>\alpha</math>]) were inhibited by <math>\geq</math> 50%. VEGFR -1,</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |

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|                                                                                      | <p>VEGFR-2, and VEGFR-3 were inhibited with 18%, 0, and 3% activity remaining relative to control, respectively.</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
| <p><b>Study #:</b><br/> <b>951-03,</b><br/> <b>951-09</b><br/> <b>and 951-41</b></p> | <p><b>Study numbers 951-03, 951-09 and 951-41 (combined review)</b></p> <p><b>Title:</b> Assessment of VEGFR-1, -2 and -3 tyrosine kinase inhibiting effect of tivozanib.<br/> <b>GLP:</b> No<br/> <b>Objectives:</b> To evaluate the autophosphorylation inhibitory activity of tivozanib on vascular endothelial growth factor receptor-1 (VEGFR-1), receptor-2 (VEGFR-2) and receptor-3 (VEGFR-3).</p> <p><b>Methods:</b></p> <ul style="list-style-type: none"> <li>• Lot Number: CDM-001</li> <li>• Cell used for VEGFR-1: Transfect Mouse Fibroblast (NIH3T3-Flt-1).</li> <li>• Cell used for VEGFR-2 and VEGFR-3: Human Umbilical Vein Endothelial Cells (HUVEC)</li> <li>• Tivozanib DMSO solution, was added to cell culture solution for final tivozanib concentrations of 0.01 nmol/L to 300 nmol/L.</li> <li>• After stimulation for 5 minutes with VEGF at a concentration of 50 ng/mL, cell extract was prepared and VEGFR-1, -2 and -3 were immunoprecipitated using anti-VEGFR-1, -2 and -3 antibodies, respectively. Immunoblotting was performed with anti-phosphorylated tyrosine antibodies to the immunoprecipitated fraction.</li> <li>• The levels of VEGFR-1, -2 and -3 tyrosine phosphorylation, and the IC<sub>50</sub> of the inhibitory activity of tivozanib on VEGFR-1, -2 and -3 autophosphorylation in this system were determined.</li> </ul> <p><b>Results:</b></p> <ul style="list-style-type: none"> <li>• Tivozanib inhibited tyrosine-phosphorylation of VEGFR-1, -2 and -3 in a concentration-dependent manner.</li> <li>• IC<sub>50</sub> for tivozanib VEGFR-1, -2 and -3 autophosphorylation was determined to be 0.21 nmol/L, 0.16 nmol/L and 0.24 nmol/L, respectively.</li> <li>• 95% confidence intervals were determined to be from 0.16 to 0.30 nmol/L, 0.13 to 0.20 nmol/L and 0.16 to 0.30 nmol/L, for VEGFR-1, -2 and -3, respectively.</li> </ul> <p><b>Conclusion:</b><br/>                 The Applicant concluded that tivozanib inhibited VEGFR-1, -2 and -3 autophosphorylation via VEGF with IC<sub>50</sub> of 0.21 nmol/L, 0.16 nmol/L and 0.24 nmol/L, respectively. The provided data supported this conclusion.</p> |
| <p><b>Study #:</b><br/> <b>951-14,</b><br/> <b>951-33</b></p>                        | <p><b>Study numbers 951-14, 951-33 and 951-27 (combined review)</b></p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |

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| <p><b>and 951-27</b></p>                                                             | <p><b>Title:</b> Evaluation of Inhibitory Activity of tivozanib hydrochloride on PDGFR <math>\beta</math>, FGFR-1 and Flt3 Receptor Tyrosine Kinase<br/> <b>GLP:</b> No<br/> <b>Objectives:</b> To evaluate the autophosphorylation inhibitory activity of tivozanib on platelet-derived growth factor receptor <math>\beta</math> (PDGFR <math>\beta</math>), fibroblast growth factor receptor-1 (FGFR-1) and fms-like tyrosine kinase 3 (Flt3) in order to investigate specificity of tivozanib on receptor tyrosine kinase.</p> <p><b>Methods:</b></p> <ul style="list-style-type: none"> <li>• Lot Number: CDM-001</li> <li>• Cell Name: Human Fibroblasts.</li> <li>• Tivozanib DMSO solution or DMSO was added to cell culture solution for final concentrations of 0.01 nmol/L to 300 nmol/L.</li> <li>• After stimulation with PDGF-BB, bFGF and FL for 5-10 minutes at concentrations of 25-100 ng/mL, cell extract was prepared and PDGF-BB was immunoprecipitated using anti-PDGFR <math>\beta</math>, anti-FGFR-1 and anti-F1t3 antibodies. Immunoblotting was performed with anti-phosphorylated tyrosine antibodies to the immunoprecipitated fraction.</li> <li>• The level of tyrosine phosphorylation, and the IC<sub>50</sub> of the inhibitory activity of tivozanib on PDGFR <math>\beta</math>, FGFR-1 and F1t3 autophosphorylation in this system were determined.</li> </ul> <p><b>Results:</b></p> <ul style="list-style-type: none"> <li>• Tivozanib inhibited tyrosine-phosphorylation of human fibroblasts PDGFR <math>\beta</math> via PDGF-BB, human fibroblasts cells via bFGF, and Flt3 via FL in a concentration-dependent manner.</li> <li>• IC<sub>50</sub> for tivozanib PDGFR <math>\beta</math>, FGFR-1 and Flt3 autophosphorylation was determined to be 1.72 nmol/L, 299 nmol/L and 422 nmol/L, respectively.</li> <li>• 95% confidence interval was determined to be from 1.39 to 2.13 nmol/L, from 214 to 417 nmol/L and from 342 to 522 nmol/L for PDGFR <math>\beta</math>, FGFR-1 and Flt3, respectively.</li> </ul> <p><b>Conclusion:</b><br/>                 The Applicant concluded that tivozanib inhibited PDGFR <math>\beta</math>, FGFR-1 and Flt3 autophosphorylation via PDGF-BB, bFGF and FL with IC<sub>50</sub> of 1.72 nmol/L, IC<sub>50</sub> of 299 nmol/L and IC<sub>50</sub> of 422 nmol/L, respectively. The provided data supported this conclusion.</p> |
| <p><b>Study #:</b><br/> <b>951-23,</b><br/> <b>951-34</b><br/> <b>and 951-36</b></p> | <p><b>Study numbers 951-23, 951-34 and 951-36 (combined review).</b></p> <p><b>Title:</b> Evaluation of Inhibitory Activity of Tivozanib Hydrochloride on c-Met, EGFR and IGF-I R Receptor Tyrosine Kinase<br/> <b>GLP:</b> No</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |

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|                                           | <p><b>Objectives:</b> To evaluate the autophosphorylation inhibitory activity of tivozanib on c-Met, EGFR and IGF-I R in order to investigate specificity of tivozanib on receptor tyrosine kinase.</p> <p><b>Methods:</b></p> <ul style="list-style-type: none"> <li>• Lot Number: CDM-001</li> <li>• Cell Name: A431 (Human Squamous Carcinoma Cells) or HT29 (Human colorectal adenocarcinoma).</li> <li>• Tivozanib DMSO solution or DMSO was added to culture medium for final concentrations of 3 nmol/L to 100 µmol/L.</li> <li>• HGF, EGF and IGF-I was added and cells were stimulated for 5-10 minutes at a final concentration of 20-50 ng/mL.</li> <li>• After stimulation, cells were immunoprecipitated using anti-c-Met, anti-EGFR or anti-IGF-I R antibodies.</li> <li>• Immunoblotting was performed with anti-phosphorylated tyrosine antibodies to the immunoprecipitated fraction.</li> <li>• The level of tyrosine phosphorylation, and the IC<sub>50</sub> of the inhibitory activity of tivozanib on c-Met, EGFR and IGF-I R autophosphorylation in this system were determined.</li> </ul> <p><b>Results:</b></p> <p><u>Study # 951-23:</u><br/>             Tivozanib inhibited tyrosine-phosphorylation of c-Met via HGF in a concentration-dependent manner. The IC<sub>50</sub> for tivozanib c-Met autophosphorylation was determined to be 1.36 µmol/L and 95% confidence interval was determined to be from 0.73 to 2.54 µmol/L.</p> <p><u>Study # 951-34 and 951-36:</u><br/>             Tivozanib did not reach 50% or greater inhibition of EGFR or IGF-I R autophosphorylation at the highest concentrations used in these studies. Precipitation in culture medium was reported with tivozanib at doses ≥ 10 µmol/L. A sigmoid concentration-inhibition curve could not be generated, therefore, IC<sub>50</sub> calculations were not established.</p> <p><b>Conclusion:</b><br/>             The Applicant concluded:</p> <ul style="list-style-type: none"> <li>• Tivozanib inhibited c-Met autophosphorylation via HGF with IC<sub>50</sub> of 1.36 µmol/L.</li> <li>• Tivozanib inhibitory activity of EGFR and of IGF-I R autophosphorylation was weak and therefore, IC<sub>50</sub> were not calculated.</li> </ul> <p>The provided data supported this conclusion.</p> |
| <p><b>Study #:</b><br/> <b>951-04</b></p> | <p><b>Title:</b> Evaluation of tivozanib hydrochloride Vascular Endothelial Cell Antiproliferative Activity</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |

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|                                          | <p><b>GLP:</b> No</p> <p><b>Objectives:</b> To evaluate the inhibitory activity of tivozanib on vascular endothelial cell proliferation via VEGF and basic fibroblast growth factor (bFGF)</p> <p><b>Methods:</b></p> <ul style="list-style-type: none"><li>• Lot Number: CDM-001</li><li>• Cell Name: human umbilical vein endothelial cells</li><li>• Tivozanib DMSO solution or DMSO was added to cell suspension for final concentrations of 0.01 to 300 nmol/L.</li><li>• VEGF or bFGF was added to human umbilical vein endothelial cells and cells were stimulated for 72 hours. [<sup>3</sup>H] thymidine was added and cultured for about 12 hours. Proliferation suppression rates were determined for each tivozanib concentration, and the IC<sub>50</sub> on vascular endothelial cell proliferation due to VEGF or bFGF in this system was established.</li></ul> <p><b>Results:</b></p> <ul style="list-style-type: none"><li>• Tivozanib resulted in inhibition of the vascular endothelial cell proliferation via VEGF at IC<sub>50</sub> determined to be 0.67 nmol/L.</li><li>• 95% confidence interval was determined to be from 0.58 to 0.77 nmol/L.</li><li>• IC<sub>50</sub> for tivozanib bFGF was determined to be ≥ 300 nmol/L.</li></ul> <p><b>Conclusion:</b><br/>The Applicant concluded that, tivozanib inhibitory activity of the vascular endothelial cell proliferation via VEGF with IC<sub>50</sub> of 0.67 nmol/L. The provided data supported this conclusion.</p> |
| <p><b>Study #:</b><br/><b>951-28</b></p> | <p><b>Title:</b> Study of Cell Growth Inhibition of tivozanib hydrochloride on Human Tumor Cells (WST-1 Assay)</p> <p><b>GLP:</b> No</p> <p><b>Objectives:</b> To evaluate the inhibitory activity of tivozanib on 8 human tumor cell strains with an antitumor nude mouse panel.</p> <p><b>Methods:</b></p> <ul style="list-style-type: none"><li>• Lot Number: CDM-001</li><li>• Cell Name: Human Lung Carcinoma A549 and Calu-6; Human Colon Carcinoma HT29, Colo205 and SW620, Human Prostate Carcinoma DU145, LNCaP and PC-3.</li><li>• Tivozanib was added to the culture medium. Cell proliferation reagent WST-1 was added and cells were cultured for additional time. Optical density of each well was measured using a microplate spectrophotometer. Cell growth rate was established at each tivozanib concentration using optical density measurements.</li></ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |

|                                           | <p><b>Results:</b></p> <ul style="list-style-type: none"> <li>Tivozanib did not affect cell tumor growth at concentrations <math>\leq 300</math> nmol/L. However, concentrations <math>\geq 1</math> <math>\mu\text{mol/L}</math> resulted in inhibition of cell tumor growth.</li> <li>The <math>\text{IC}_{50}</math> for the different cells were established to be:</li> </ul> <table border="1" data-bbox="362 411 1446 548"> <thead> <tr> <th></th> <th>A549</th> <th>Calu-6</th> <th>HT29</th> <th>Colo205</th> <th>SW620</th> <th>DU145</th> <th>LNCaP</th> <th>PC-3</th> </tr> </thead> <tbody> <tr> <td><math>\text{IC}_{50}</math> (<math>\mu\text{mol/L}</math>)</td> <td><math>\geq 10</math></td> <td><math>\geq 10</math></td> <td><math>\geq 3</math></td> <td><math>\geq 3</math></td> <td><math>\geq 3</math></td> <td><math>\geq 10</math></td> <td><math>\geq 1</math></td> <td><math>\geq 3</math></td> </tr> </tbody> </table> <p><b>Conclusion:</b><br/>                     The Applicant concluded that tivozanib at concentrations <math>\geq 1</math> <math>\mu\text{mol/L}</math> resulted in inhibition of cell tumor growth at 8 human tumor cell strains. The data provided support this conclusion.</p>                                                                                                                                                                                                                                                                                                                                                                                       |           | A549     | Calu-6   | HT29     | Colo205   | SW620    | DU145    | LNCaP | PC-3 | $\text{IC}_{50}$ ( $\mu\text{mol/L}$ ) | $\geq 10$ | $\geq 10$ | $\geq 3$ | $\geq 3$ | $\geq 3$ | $\geq 10$ | $\geq 1$ | $\geq 3$ |
|-------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------|----------|----------|----------|-----------|----------|----------|-------|------|----------------------------------------|-----------|-----------|----------|----------|----------|-----------|----------|----------|
|                                           | A549                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | Calu-6    | HT29     | Colo205  | SW620    | DU145     | LNCaP    | PC-3     |       |      |                                        |           |           |          |          |          |           |          |          |
| $\text{IC}_{50}$ ( $\mu\text{mol/L}$ )    | $\geq 10$                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | $\geq 10$ | $\geq 3$ | $\geq 3$ | $\geq 3$ | $\geq 10$ | $\geq 1$ | $\geq 3$ |       |      |                                        |           |           |          |          |          |           |          |          |
| <p><b>Study #:</b><br/> <b>951-16</b></p> | <p><b>Title:</b> Evaluation of inhibitory activity of tivozanib hydrochloride on c-Kit receptor Tyrosine Kinase<br/> <b>GLP:</b> No<br/> <b>Objectives:</b> To evaluate the autophosphorylation inhibitory activity of tivozanib on c-Kit receptor Tyrosine Kinase. c-Kit tyrosine kinase, which belongs to the PDGFR family, in which structure of the tyrosine kinase domain is analogous to that of VEGFR, was evaluated in order to investigate specificity of tivozanib on VEGFR tyrosine kinase.</p> <p><b>Methods:</b></p> <ul style="list-style-type: none"> <li>Lot Number: CDM-001</li> <li>Cell Name: Ku812-F (Chronic myelogenous leukemia)</li> <li>Tivozanib DMSO solution or DMSO was added to cell culture solution for final concentrations of 0.01 to 300 nmol/L.</li> <li>Recombinant Human Stem Cell Factor was added and cells were stimulated for 15 minutes at a final concentration of 100 ng/mL.</li> <li>After stimulation, cell extract was prepared and c-Kit was immunoprecipitated using anti-c-Kit antibodies. Immunoblotting was performed with anti-phosphorylated tyrosine antibodies to the immunoprecipitated fraction. The level of c-Kit tyrosine phosphorylation accompanying stimulation was analyzed.</li> </ul> <p><b>Results:</b><br/>                     Tivozanib inhibited tyrosine-phosphorylation of c-Kit via SCF in a concentration-dependent manner and <math>\text{IC}_{50}</math> for tivozanib c-Kit autophosphorylation was determined to be 1.63 nmol/L and the 95% confidence interval was determined to be from 1.13 to 2.35 nmol/L.</p> <p><b>Conclusion:</b></p> |           |          |          |          |           |          |          |       |      |                                        |           |           |          |          |          |           |          |          |

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|                                          | <p>The Applicant concluded that, tivozanib inhibited c-Kit autophosphorylation via SCF with IC<sub>50</sub> of 1.63 nmol/L. The provided data supported this conclusion.</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
| <p><b>Study #:</b><br/><b>951-31</b></p> | <p><b>Title:</b> Antitumor Efficacy of tivozanib hydrochloride on the Nude Rat Subcutaneously-Implanted Human Lung Carcinoma A549<br/> <b>GLP:</b> No<br/> <b>Objectives:</b> To evaluate the angiogenesis inhibitory activity of tivozanib, using a nude rat model implanted with human lung carcinoma A549</p> <p><b>Methods:</b></p> <ul style="list-style-type: none"> <li>• Human lung carcinoma A549 tumor cells were implanted by subcutaneous injection to female nude rats (F344/N Jcl-rnu).</li> <li>• Treatment: orally administered once daily at dosages of 0.04, 0.2 and 1 mg/kg/day (Lot# CDM-001) for a continuous 7- day period.</li> <li>• Tumors were extracted the day following the final administration, were then sectioned and immunostained with anti-rat CD31 antibodies or stained with H&amp;E.</li> <li>• Endpoints evaluated: tumor volumes were measured twice a week, daily body weight and tumor condition were recorded twice weekly.</li> </ul> <p><b>Results:</b></p> <ul style="list-style-type: none"> <li>• Dosing at 1 mg/kg/day resulted in a significant inhibition of intratumor vascular endothelial cell density (2.01% vs. 9.22% in the control group).</li> <li>• Dosing at 1 mg/kg/day resulted in a decrease in tumor volume (22% and 40% on days 4 and 7, respectively), and showed tumor antiproliferative activity with inhibition of tumor growth of 50% or greater.</li> <li>• Regression activity of 23% was reported at 1 mg/kg/day.</li> </ul> <p><b>Conclusion:</b><br/>                 The Applicant concluded that tivozanib administered orally at 1 mg/kg/day for 7 days resulted in inhibition of intratumor angiogenesis in the implanted human lung carcinoma A549 nude rat. The provided data supported this conclusion.</p> |
| <p><b>Study #:</b><br/><b>951-38</b></p> | <p><b>Title:</b> Angiogenesis and Vascular Permeability Suppression Activity of tivozanib hydrochloride on Nude Rat Subcutaneously-Implanted Human Lung Carcinoma A549<br/> <b>GLP:</b> No<br/> <b>Objectives:</b> To evaluate the angiogenesis and vascular permeability of tumors using the Evans blue (dye) method after treatment of nude rat implanted with human lung carcinoma A549 with tivozanib.</p> <p><b>Methods:</b></p> <ul style="list-style-type: none"> <li>• Human lung carcinoma A549 tumor cells were implanted by subcutaneous injection to female nude rats (F344/N Jcl-rnu).</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |

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|                                                | <ul style="list-style-type: none"> <li>• Treatment: orally administered once daily at dosages of 0.04, 0.2, and 1 mg/kg/day (Lot# CDM-001) for a continuous 7- day period. Six rats per group were used.</li> <li>• Evans blue was intravenously administered (10 mg/mL) for four hours post the last dose on day 7 and rats were sacrificed 30 minutes after.</li> <li>• Optical density was measured on homogenized tumor tissues with spectrophotometer.</li> <li>• Endpoints evaluated: quantity of Evans blue in tumor tissues.</li> </ul> <p><b>Results and Conclusion:</b><br/>                 The Applicant concludes that tivozanib administered orally at 0.2 and 1 mg/kg/day for 7 days showed inhibition of angiogenesis and vascular permeability in implanted human lung carcinoma A549 nude rat model. This was demonstrated by the significant decrease of 35% and 59% in the quantity of Evans blue dye reported at 0.2 and 1 mg/kg/day, respectively, in tumor tissues. The data provided supported this conclusion.</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
| <p><b>Study #:</b><br/> <b>AV951-08008</b></p> | <p><b>Title:</b> Tivozanib hydrochloride PD Analysis in Nude Mice Bearing Murine Breast HER2 Xenograft Tumors after Continuous Daily Oral Dosing of 5 mg/kg or 20 mg/kg<br/> <b>GLP:</b> No<br/> <b>Objectives:</b> To determine the effects of tivozanib on tumor microvasculature, cell proliferation, and hypoxia in the mouse breast HER2 tumor model.</p> <p><b>Methods:</b></p> <ul style="list-style-type: none"> <li>• BH505 mouse breast HER2 tumor cells were implanted by subcutaneous injection to female nude mice (NCr nu/nu).</li> <li>• Treatment: orally administered once daily; control (0.5% methylcellulose), 5, and 20 mg/kg/day (Lot# CDM-003) for a continuous 2 to 5 day period. Twelve mice per group were used.</li> <li>• Endpoints evaluated: Tumors were measured at 48, 72, 96 and 120 hours post initiation of dosing. H&amp;E staining was used for histopathologically evaluation; immunohistochemistry staining (CD31 stain) was used to determine the % of viable tissue area microvasculature density to determine vessel number per viable tumor area; and cell proliferation rate (KI67) and tumor hypoxia (HIF1-<math>\alpha</math> protein level) were determined using ELISA.</li> </ul> <p><b>Results:</b></p> <ul style="list-style-type: none"> <li>• Doses <math>\geq</math> 5 mg/kg/day, resulted in a significant decrease in viable tumor area following 2 days of treatment. Viable tumor areas were significantly smaller at 20 mg/kg/day in comparison with 5 mg/kg/day, at all time points examined.</li> <li>• At 20 mg/kg/day, a decrease in cell proliferation rate was reported at 72 and 96 hours time points.</li> </ul> |

|                                                   | <ul style="list-style-type: none"> <li>• At doses <math>\geq 5</math> mg/kg/day, the total number of proliferating cells was significantly lower at all time points examined.</li> <li>• Doses <math>\geq 5</math> mg/kg/day resulted in significant decreases in vessel cross-section area and microvascular density at all time points examined.</li> <li>• Doses <math>\geq 5</math> mg/kg/day resulted in an increase in tumor hypoxia as measured by HIF1-<math>\alpha</math> protein. The highest levels were reported at the 120-hour time point.</li> </ul> <p><b>Conclusion:</b><br/>                 The Applicant concluded that tivozanib administered in a repeat-dose manner resulted in inhibition of tumor angiogenesis and tumor cell proliferation. The data provided supported Applicant’s conclusion.</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |           |       |          |   |                      |      |         |    |                      |      |         |    |                         |                      |         |    |                                                   |                                               |         |    |
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| <p><b>Study #:</b><br/> <b>AV951-08195</b></p>    | <p><b>Title:</b> Tivozanib Antitumor Activity as Monotherapy or in Combination with Rapamycin in ICR/SCID Mice Bearing Human Renal Cell Carcinoma 786-0 Xenograft Tumors</p> <p><b>GLP:</b> No</p> <p><b>Objectives:</b> To determine the effects of tivozanib (AV-951) alone and in combination with rapamycin on tumor growth, angiogenesis and cell proliferation after continuous daily oral dosing.</p> <p><b>Methods:</b><br/>                 Human renal cell carcinoma 786-0 tumor cells were implanted by subcutaneous injection to female ICR SCID mice. Mice were treated daily as listed below:</p> <p><b>Study Design:</b></p> <table border="1" data-bbox="363 1230 1450 1545"> <thead> <tr> <th>Treatment</th> <th>Route</th> <th>Duration</th> <th>N</th> </tr> </thead> <tbody> <tr> <td>0.5% methylcellulose</td> <td>Oral</td> <td>28 days</td> <td>10</td> </tr> <tr> <td>AV-951 (5 mg/kg/day)</td> <td>Oral</td> <td>79 days</td> <td>10</td> </tr> <tr> <td>Rapamycin (1 mg/kg/day)</td> <td>Intraperitoneal (ip)</td> <td>31 days</td> <td>10</td> </tr> <tr> <td>AV-951 (5 mg/kg/day) Plus Rapamycin (1 mg/kg/day)</td> <td>Oral (AV-951) and Intraperitoneal (Rapamycin)</td> <td>79 days</td> <td>10</td> </tr> </tbody> </table> <p>Endpoints evaluated: Body weight, tumor measurements, angiogenesis and tumor cell proliferation were analyzed using histopathology (H&amp;E staining) to determine the % of viable tissue area, immunohistochemistry staining to determine microvasculature density (CD31 stain) to assess vessel number per viable tumor area, and cell proliferation rate (using KI67)</p> <p><b>Results:</b></p> | Treatment | Route | Duration | N | 0.5% methylcellulose | Oral | 28 days | 10 | AV-951 (5 mg/kg/day) | Oral | 79 days | 10 | Rapamycin (1 mg/kg/day) | Intraperitoneal (ip) | 31 days | 10 | AV-951 (5 mg/kg/day) Plus Rapamycin (1 mg/kg/day) | Oral (AV-951) and Intraperitoneal (Rapamycin) | 79 days | 10 |
| Treatment                                         | Route                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | Duration  | N     |          |   |                      |      |         |    |                      |      |         |    |                         |                      |         |    |                                                   |                                               |         |    |
| 0.5% methylcellulose                              | Oral                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | 28 days   | 10    |          |   |                      |      |         |    |                      |      |         |    |                         |                      |         |    |                                                   |                                               |         |    |
| AV-951 (5 mg/kg/day)                              | Oral                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | 79 days   | 10    |          |   |                      |      |         |    |                      |      |         |    |                         |                      |         |    |                                                   |                                               |         |    |
| Rapamycin (1 mg/kg/day)                           | Intraperitoneal (ip)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | 31 days   | 10    |          |   |                      |      |         |    |                      |      |         |    |                         |                      |         |    |                                                   |                                               |         |    |
| AV-951 (5 mg/kg/day) Plus Rapamycin (1 mg/kg/day) | Oral (AV-951) and Intraperitoneal (Rapamycin)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | 79 days   | 10    |          |   |                      |      |         |    |                      |      |         |    |                         |                      |         |    |                                                   |                                               |         |    |

|                                                |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
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|                                                | <ul style="list-style-type: none"> <li>• Two mice in the combination treatment group were found dead on days 47 and 52.</li> <li>• No test article-related effects on body weights were reported.</li> <li>• Treatment at 5 mg/kg/day AV-951 resulted in 86% decrease in tumor volume throughout the entire period (day 126).</li> <li>• At 1 mg/kg/day, treatment with Rapamycin resulted in slowing tumor progression, resulting in 86% tumor growth inhibition. In contrast to tumors treated with AV-951, however, tumors continued to grow and no decrease in tumor volume was reported.</li> <li>• The combination of AV-951 (5 mg/kg/day) and Rapamycin (1 mg/kg/day) resulted in 86% decrease in tumor volume.</li> <li>• The combination of AV-951 (5 mg/kg/day) and Rapamycin (1 mg/kg/day) resulted in the total viable tumor area of 15.4% and 57.2% for AV-951 monotherapy.</li> <li>• The combined treatment resulted in a significant decrease (84%) in the number of microvessels per viable tumor area in comparison to the monotherapy.</li> <li>• The combined treatment resulted in a significant decrease (55%) in cellular proliferation index comparison to monotherapy.</li> </ul> <p><b>Conclusion:</b><br/>                 The Applicant concludes that the combined treatment showed greater effect on tumor growth, angiogenesis, and cell proliferation. This data provided supports the Applicant’s conclusion.</p> |
| <p><b>Study #:</b><br/> <b>AV951-08048</b></p> | <p><b>Title:</b> AV-951: Antitumor Activity of AV-951 in a Murine Lung KRAS Tumor Xenograft Model<br/> <b>GLP:</b> No<br/> <b>Objectives:</b> To determine the degree of tumor regression of LK216 tumor xenografts in SCID mice treated with AV-951.</p> <p><b>Methods:</b></p> <ul style="list-style-type: none"> <li>• Animals: Tumor cells LK216 (murine lung KRAS tumor) were implanted by subcutaneous injection to female SCID mice (5/group)</li> <li>• Treatment: Orally, once daily (0.5% methylcellulose, AV-951 at 5 and 20 mg/kg/day) for 14 days. Animals were sacrificed on Day 36.</li> <li>• Endpoints evaluated: Body weight, tumor size (measured twice a week for 2 weeks).</li> </ul> <p><b>Results:</b></p> <ul style="list-style-type: none"> <li>• All animals survived to scheduled termination. At doses <math>\geq</math> 5 mg/kg/day, significant tumor regression was evident, as was a decrease in mean tumor volume on Day 36 (81% and 86% at 5 and 20 mg/kg/day, respectively).</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                         |

|                                                                                                                                                                                                                                     | <p><b>Conclusion:</b><br/>                 The Applicant concludes that treatment at doses up to 20 mg/kg/day resulted in tumor regression of LK216 tumor xenografts in SCID mice. The data provided supported the Applicant's conclusion.</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |                    |      |       |         |       |         |       |      |       |   |    |    |    |    |    |    |    |     |    |    |    |    |    |    |    |    |     |
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| <p><b>Study #:</b><br/>                 951-24,<br/>                 951-08,<br/>                 951-05,<br/>                 951-06,<br/>                 951-25,<br/>                 951-11<br/>                 and 951-12</p> | <p><b>Study numbers 951-24, 951-08, 951-05, 951-06, 951-25, 951-11 and 951-12 (combined review of these studies).</b></p> <p><b>Title:</b> Antitumor Activity of AV-951 Administered Orally in Nude Mouse Bearing Subcutaneous Human Tumors<br/> <b>GLP:</b> No<br/> <b>Objectives:</b><br/>                 To investigate antitumor activity of the AV-951 compound administered orally in a panel of 8 human subcutaneously xenografted tumor models in nude mice.</p> <p><b>Methods:</b></p> <ul style="list-style-type: none"> <li>Human Lung Carcinoma (A549, Calu6), colon cancer (HT29, SW620, COLO205) and prostate carcinoma (DU145, PC-3, LNCap) tumor cells were implanted by subcutaneous injection to female BALB/cAJcl-nu mice (5/group).</li> <li>Lot Number: CM-001</li> <li>Treatment: Orally, once daily (0.5% methylcellulose, AV-951 at 5 and 20 mg/kg/day) for 14 days. Animals were sacrificed on Day 29.</li> <li>Endpoints evaluated: Body weight, tumor volume, tumor weight, antitumor efficacy, tumor antiproliferative activity and tumor regression.</li> </ul> <p><b>Results:</b><br/>                 AV-951 at 5 and 20 mg/kg/day resulted in tumor growth inhibition of all cell lines tested (8 cell lines), with a greater inhibition at 20 mg/kg/day. Regression was not reported in either dosing groups for tumor cells A549, Calu6, HT29, SW620, COLO205, PC-3, LNCap, but was reported for DU145 tumor cells.</p> <p><i>Summary of % tumor growth inhibition in different cell lines:</i></p> <table border="1" data-bbox="362 1501 1463 1661"> <thead> <tr> <th>AV-951 (mg/kg/day)</th> <th>A549</th> <th>Calu6</th> <th>HT29</th> <th>SW620</th> <th>COLO205</th> <th>DU145</th> <th>PC-3</th> <th>LNCap</th> </tr> </thead> <tbody> <tr> <td>5</td> <td>68</td> <td>56</td> <td>79</td> <td>52</td> <td>75</td> <td>53</td> <td>81</td> <td>114</td> </tr> <tr> <td>20</td> <td>92</td> <td>64</td> <td>87</td> <td>74</td> <td>98</td> <td>44</td> <td>66</td> <td>122</td> </tr> </tbody> </table> <p><b>Conclusion:</b><br/>                 The Applicant concludes that oral treatment with AV-951 at 5 and 20 mg/kg/day for 14 days resulted in tumor growth inhibition of a panel of 8 human cancer cell lines (lung, prostate and colon) implanted in nude mice. The data provided supported this conclusion.</p> | AV-951 (mg/kg/day) | A549 | Calu6 | HT29    | SW620 | COLO205 | DU145 | PC-3 | LNCap | 5 | 68 | 56 | 79 | 52 | 75 | 53 | 81 | 114 | 20 | 92 | 64 | 87 | 74 | 98 | 44 | 66 | 122 |
| AV-951 (mg/kg/day)                                                                                                                                                                                                                  | A549                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | Calu6              | HT29 | SW620 | COLO205 | DU145 | PC-3    | LNCap |      |       |   |    |    |    |    |    |    |    |     |    |    |    |    |    |    |    |    |     |
| 5                                                                                                                                                                                                                                   | 68                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | 56                 | 79   | 52    | 75      | 53    | 81      | 114   |      |       |   |    |    |    |    |    |    |    |     |    |    |    |    |    |    |    |    |     |
| 20                                                                                                                                                                                                                                  | 92                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | 64                 | 87   | 74    | 98      | 44    | 66      | 122   |      |       |   |    |    |    |    |    |    |    |     |    |    |    |    |    |    |    |    |     |

| <p><b>Study #:</b><br/> <b>PRT/0214</b><br/> <b>9-1</b></p> | <p><b>Title:</b> Antitumor Activity of KRN951 Administered orally in Nude Rats Bearing subcutaneous Human Tumors</p> <p><b>GLP:</b> No</p> <p><b>Objectives:</b> To investigate antitumor activity of the KRN951 compound administered orally in a panel of 14 human subcutaneously xenografted tumor models in nude rats.</p> <p><b>Methods:</b></p> <ul style="list-style-type: none"> <li>• <b>Cell lines:</b> BxPC-3, Caki-1, Calu-6, CG-9, DU 145, LoVo, LS 174T, MDA-MB-231, NCI-H460, OVCAR-3, PC-3, SK-HEP-1, SK-OV-3 and ZR-75-1.</li> </ul> <table border="1" style="margin-left: 40px;"> <thead> <tr> <th>Cell lines</th> <th>Type</th> <th>References</th> </tr> </thead> <tbody> <tr> <td>BxPC-3</td> <td>Pancreas adenocarcinoma</td> <td>(1)</td> </tr> <tr> <td>Caki-1</td> <td>Kidney cell carcinoma</td> <td>(2)</td> </tr> <tr> <td>Calu-6</td> <td>Lung carcinoma</td> <td>(3)</td> </tr> <tr> <td>CGL-9</td> <td>Glioma</td> <td>(4)</td> </tr> <tr> <td>DU 145</td> <td>Human prostate carcinoma</td> <td>(5)</td> </tr> <tr> <td>LoVo</td> <td>Colon adenocarcinoma</td> <td>(6)</td> </tr> </tbody> </table> <table border="1" style="margin-left: 40px;"> <thead> <tr> <th>Cell lines</th> <th>Type</th> <th>References</th> </tr> </thead> <tbody> <tr> <td>LS 174T</td> <td>Colon adenocarcinoma</td> <td>(7)</td> </tr> <tr> <td>MDA-MB-231</td> <td>Breast carcinoma</td> <td>(8)</td> </tr> <tr> <td>NCI-H460</td> <td>Lung carcinoma</td> <td>(9)</td> </tr> <tr> <td>OVCAR-3</td> <td>Ovarian adenocarcinoma</td> <td>(10)</td> </tr> <tr> <td>PC-3</td> <td>Prostate carcinoma</td> <td>(11)</td> </tr> <tr> <td>SK-HEP-1</td> <td>Liver adenocarcinoma</td> <td>(12)</td> </tr> <tr> <td>SK-OV-3</td> <td>Ovarian carcinoma</td> <td>(13)</td> </tr> <tr> <td>ZR-75-1</td> <td>Breast from ductal adenocarcinoma</td> <td>(14)</td> </tr> </tbody> </table> <p style="margin-left: 40px;"><i>(excerpted from Applicant's report)</i></p> <ul style="list-style-type: none"> <li>• Animals: Male and female RH-nu/nu rats</li> <li>• Radiation treatment: Whole body irradiation with a gama-source (7 Gy)</li> <li>• Groups: 3-6 rats/group</li> <li>• Lot Number: CM-001</li> <li>• Subcutaneous injection – implantation of tumor cells</li> <li>• Treatment: Orally, once daily (0.5% methylcellulose, KRN951 at 0.2 and 1 mg/kg/day) for 14 days. Animals were sacrificed on day 29.</li> <li>• Endpoints evaluated: Body weight and tumor size were measured.</li> </ul> | Cell lines | Type | References | BxPC-3 | Pancreas adenocarcinoma | (1) | Caki-1 | Kidney cell carcinoma | (2) | Calu-6 | Lung carcinoma | (3) | CGL-9 | Glioma | (4) | DU 145 | Human prostate carcinoma | (5) | LoVo | Colon adenocarcinoma | (6) | Cell lines | Type | References | LS 174T | Colon adenocarcinoma | (7) | MDA-MB-231 | Breast carcinoma | (8) | NCI-H460 | Lung carcinoma | (9) | OVCAR-3 | Ovarian adenocarcinoma | (10) | PC-3 | Prostate carcinoma | (11) | SK-HEP-1 | Liver adenocarcinoma | (12) | SK-OV-3 | Ovarian carcinoma | (13) | ZR-75-1 | Breast from ductal adenocarcinoma | (14) |
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| Cell lines                                                  | Type                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | References |      |            |        |                         |     |        |                       |     |        |                |     |       |        |     |        |                          |     |      |                      |     |            |      |            |         |                      |     |            |                  |     |          |                |     |         |                        |      |      |                    |      |          |                      |      |         |                   |      |         |                                   |      |
| BxPC-3                                                      | Pancreas adenocarcinoma                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | (1)        |      |            |        |                         |     |        |                       |     |        |                |     |       |        |     |        |                          |     |      |                      |     |            |      |            |         |                      |     |            |                  |     |          |                |     |         |                        |      |      |                    |      |          |                      |      |         |                   |      |         |                                   |      |
| Caki-1                                                      | Kidney cell carcinoma                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | (2)        |      |            |        |                         |     |        |                       |     |        |                |     |       |        |     |        |                          |     |      |                      |     |            |      |            |         |                      |     |            |                  |     |          |                |     |         |                        |      |      |                    |      |          |                      |      |         |                   |      |         |                                   |      |
| Calu-6                                                      | Lung carcinoma                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | (3)        |      |            |        |                         |     |        |                       |     |        |                |     |       |        |     |        |                          |     |      |                      |     |            |      |            |         |                      |     |            |                  |     |          |                |     |         |                        |      |      |                    |      |          |                      |      |         |                   |      |         |                                   |      |
| CGL-9                                                       | Glioma                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | (4)        |      |            |        |                         |     |        |                       |     |        |                |     |       |        |     |        |                          |     |      |                      |     |            |      |            |         |                      |     |            |                  |     |          |                |     |         |                        |      |      |                    |      |          |                      |      |         |                   |      |         |                                   |      |
| DU 145                                                      | Human prostate carcinoma                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | (5)        |      |            |        |                         |     |        |                       |     |        |                |     |       |        |     |        |                          |     |      |                      |     |            |      |            |         |                      |     |            |                  |     |          |                |     |         |                        |      |      |                    |      |          |                      |      |         |                   |      |         |                                   |      |
| LoVo                                                        | Colon adenocarcinoma                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | (6)        |      |            |        |                         |     |        |                       |     |        |                |     |       |        |     |        |                          |     |      |                      |     |            |      |            |         |                      |     |            |                  |     |          |                |     |         |                        |      |      |                    |      |          |                      |      |         |                   |      |         |                                   |      |
| Cell lines                                                  | Type                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | References |      |            |        |                         |     |        |                       |     |        |                |     |       |        |     |        |                          |     |      |                      |     |            |      |            |         |                      |     |            |                  |     |          |                |     |         |                        |      |      |                    |      |          |                      |      |         |                   |      |         |                                   |      |
| LS 174T                                                     | Colon adenocarcinoma                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | (7)        |      |            |        |                         |     |        |                       |     |        |                |     |       |        |     |        |                          |     |      |                      |     |            |      |            |         |                      |     |            |                  |     |          |                |     |         |                        |      |      |                    |      |          |                      |      |         |                   |      |         |                                   |      |
| MDA-MB-231                                                  | Breast carcinoma                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | (8)        |      |            |        |                         |     |        |                       |     |        |                |     |       |        |     |        |                          |     |      |                      |     |            |      |            |         |                      |     |            |                  |     |          |                |     |         |                        |      |      |                    |      |          |                      |      |         |                   |      |         |                                   |      |
| NCI-H460                                                    | Lung carcinoma                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | (9)        |      |            |        |                         |     |        |                       |     |        |                |     |       |        |     |        |                          |     |      |                      |     |            |      |            |         |                      |     |            |                  |     |          |                |     |         |                        |      |      |                    |      |          |                      |      |         |                   |      |         |                                   |      |
| OVCAR-3                                                     | Ovarian adenocarcinoma                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | (10)       |      |            |        |                         |     |        |                       |     |        |                |     |       |        |     |        |                          |     |      |                      |     |            |      |            |         |                      |     |            |                  |     |          |                |     |         |                        |      |      |                    |      |          |                      |      |         |                   |      |         |                                   |      |
| PC-3                                                        | Prostate carcinoma                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | (11)       |      |            |        |                         |     |        |                       |     |        |                |     |       |        |     |        |                          |     |      |                      |     |            |      |            |         |                      |     |            |                  |     |          |                |     |         |                        |      |      |                    |      |          |                      |      |         |                   |      |         |                                   |      |
| SK-HEP-1                                                    | Liver adenocarcinoma                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | (12)       |      |            |        |                         |     |        |                       |     |        |                |     |       |        |     |        |                          |     |      |                      |     |            |      |            |         |                      |     |            |                  |     |          |                |     |         |                        |      |      |                    |      |          |                      |      |         |                   |      |         |                                   |      |
| SK-OV-3                                                     | Ovarian carcinoma                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | (13)       |      |            |        |                         |     |        |                       |     |        |                |     |       |        |     |        |                          |     |      |                      |     |            |      |            |         |                      |     |            |                  |     |          |                |     |         |                        |      |      |                    |      |          |                      |      |         |                   |      |         |                                   |      |
| ZR-75-1                                                     | Breast from ductal adenocarcinoma                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | (14)       |      |            |        |                         |     |        |                       |     |        |                |     |       |        |     |        |                          |     |      |                      |     |            |      |            |         |                      |     |            |                  |     |          |                |     |         |                        |      |      |                    |      |          |                      |      |         |                   |      |         |                                   |      |

|                                                    | <p><b>Results:</b><br/>                 KRN951 at 0.2 and 1 mg/kg/day resulted in tumor growth inhibition of all cell lines tested (14 cell lines), with a greater inhibition at 1 mg/kg/day.<br/>                 The following table summaries the % tumor growth inhibition in different cell lines:</p> <table border="1" data-bbox="376 428 1459 546"> <thead> <tr> <th></th> <th>BxPC-3</th> <th>Caki-1</th> <th>Calu-6</th> <th>CGL-9</th> <th>DU 145</th> <th>LoVo</th> <th>LS 174T</th> </tr> </thead> <tbody> <tr> <td>KRN 951 0.2 mg/kg</td> <td>61</td> <td>27</td> <td>44</td> <td>46</td> <td>90</td> <td>60</td> <td>86</td> </tr> <tr> <td>KRN 951 1.0 mg/kg</td> <td>94</td> <td>&gt;100</td> <td>99</td> <td>96</td> <td>&gt;100</td> <td>&gt;100</td> <td>100</td> </tr> </tbody> </table><br><table border="1" data-bbox="365 604 1471 722"> <thead> <tr> <th></th> <th>MDA-MB-231</th> <th>NCI-H460</th> <th>OVCAR-3</th> <th>PC-3</th> <th>SK-HEP-1</th> <th>SK-OV-3</th> <th>ZR-75-1</th> </tr> </thead> <tbody> <tr> <td>KRN 951 0.2 mg/kg</td> <td>77</td> <td>69</td> <td>25</td> <td>74</td> <td>60</td> <td>93</td> <td>77</td> </tr> <tr> <td>KRN 951 1.0 mg/kg</td> <td>&gt;100</td> <td>86</td> <td>99</td> <td>96</td> <td>90</td> <td>99</td> <td>94</td> </tr> </tbody> </table> <p><i>(excerpted from Applicant's report)</i></p> <p><b>Conclusion:</b><br/>                 The Applicant concludes that KRN951 administered orally at 0.2 and 1 mg/kg/day for 14 days resulted in tumor growth inhibition of a panel of 14 human cancer cell lines (pancreas, kidney, lung, glioma, prostate, colon, breast, ovary and liver) implanted in nude rats. The data provided supported this conclusion.</p> |          | BxPC-3  | Caki-1 | Calu-6   | CGL-9   | DU 145  | LoVo | LS 174T | KRN 951 0.2 mg/kg | 61 | 27 | 44 | 46 | 90 | 60 | 86 | KRN 951 1.0 mg/kg | 94 | >100 | 99 | 96 | >100 | >100 | 100 |  | MDA-MB-231 | NCI-H460 | OVCAR-3 | PC-3 | SK-HEP-1 | SK-OV-3 | ZR-75-1 | KRN 951 0.2 mg/kg | 77 | 69 | 25 | 74 | 60 | 93 | 77 | KRN 951 1.0 mg/kg | >100 | 86 | 99 | 96 | 90 | 99 | 94 |
|----------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------|---------|--------|----------|---------|---------|------|---------|-------------------|----|----|----|----|----|----|----|-------------------|----|------|----|----|------|------|-----|--|------------|----------|---------|------|----------|---------|---------|-------------------|----|----|----|----|----|----|----|-------------------|------|----|----|----|----|----|----|
|                                                    | BxPC-3                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | Caki-1   | Calu-6  | CGL-9  | DU 145   | LoVo    | LS 174T |      |         |                   |    |    |    |    |    |    |    |                   |    |      |    |    |      |      |     |  |            |          |         |      |          |         |         |                   |    |    |    |    |    |    |    |                   |      |    |    |    |    |    |    |
| KRN 951 0.2 mg/kg                                  | 61                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | 27       | 44      | 46     | 90       | 60      | 86      |      |         |                   |    |    |    |    |    |    |    |                   |    |      |    |    |      |      |     |  |            |          |         |      |          |         |         |                   |    |    |    |    |    |    |    |                   |      |    |    |    |    |    |    |
| KRN 951 1.0 mg/kg                                  | 94                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | >100     | 99      | 96     | >100     | >100    | 100     |      |         |                   |    |    |    |    |    |    |    |                   |    |      |    |    |      |      |     |  |            |          |         |      |          |         |         |                   |    |    |    |    |    |    |    |                   |      |    |    |    |    |    |    |
|                                                    | MDA-MB-231                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | NCI-H460 | OVCAR-3 | PC-3   | SK-HEP-1 | SK-OV-3 | ZR-75-1 |      |         |                   |    |    |    |    |    |    |    |                   |    |      |    |    |      |      |     |  |            |          |         |      |          |         |         |                   |    |    |    |    |    |    |    |                   |      |    |    |    |    |    |    |
| KRN 951 0.2 mg/kg                                  | 77                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | 69       | 25      | 74     | 60       | 93      | 77      |      |         |                   |    |    |    |    |    |    |    |                   |    |      |    |    |      |      |     |  |            |          |         |      |          |         |         |                   |    |    |    |    |    |    |    |                   |      |    |    |    |    |    |    |
| KRN 951 1.0 mg/kg                                  | >100                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | 86       | 99      | 96     | 90       | 99      | 94      |      |         |                   |    |    |    |    |    |    |    |                   |    |      |    |    |      |      |     |  |            |          |         |      |          |         |         |                   |    |    |    |    |    |    |    |                   |      |    |    |    |    |    |    |
| <p><b>Study #:</b><br/>                 951-39</p> | <p><b>Title:</b> Antitumor Effect of KRN951 Long Term Dosing and Intermittent Dosing of Nude Mice Subcutaneously-Implanted Human Prostate Carcinoma (Cell Line DU145)<br/> <b>GLP:</b> No<br/> <b>Objectives:</b> To investigate antitumor efficacy in a subcutaneously-implanted prostate carcinoma DU145 nude mouse model treated with KRN951.</p> <p><b>Methods:</b></p> <ul style="list-style-type: none"> <li>• Cell: Human prostate carcinoma DU145</li> <li>• Animals: male BALB/cAJcl-nu mice</li> <li>• Tumor cells were implanted by subcutaneous injection.</li> <li>• Treatment: Orally.</li> </ul> <p><b>Dosing schedule:</b></p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |          |         |        |          |         |         |      |         |                   |    |    |    |    |    |    |    |                   |    |      |    |    |      |      |     |  |            |          |         |      |          |         |         |                   |    |    |    |    |    |    |    |                   |      |    |    |    |    |    |    |

|                                                | <table border="1"> <thead> <tr> <th>Group</th> <th>Dose Amount</th> <th>Dose Period</th> <th>Mice</th> </tr> </thead> <tbody> <tr> <td>A</td> <td>Media</td> <td>10 weeks</td> <td>8</td> </tr> <tr> <td>B</td> <td>KRN951 2 mg / kg</td> <td>10 weeks</td> <td>8</td> </tr> <tr> <td>C</td> <td>KRN951 20 mg / kg</td> <td>10 weeks</td> <td>8</td> </tr> <tr> <td>D</td> <td>KRN951 2 mg / kg</td> <td>2 weeks dose + 2 weeks no dose x 3</td> <td>8</td> </tr> <tr> <td>E</td> <td>KRN951 20 mg / kg</td> <td>2 weeks dose + 2 weeks no dose x 3</td> <td>8</td> </tr> <tr> <td>F</td> <td>KRN951 2 mg / kg</td> <td>4 weeks dose + 2 weeks no dose x 2</td> <td>8</td> </tr> <tr> <td>G</td> <td>KRN951 20 mg / kg</td> <td>4 weeks dose + 2 weeks no dose x 2</td> <td>8</td> </tr> </tbody> </table> <p><i>(excerpted from Applicant's report)</i></p> <ul style="list-style-type: none"> <li>• Schedule #1 was a 2 and 20 mg/kg dose of KRN951 per day for 10 weeks.</li> <li>• Schedule #2 was a cycle of 2 and 20 mg/kg dose of KRN951 per day for two weeks, then no dosing for two weeks, repeated three times.</li> <li>• Schedule #3 was a cycle of 2 and 20 mg/kg dose of KRN951 per day for four weeks, then no dosing for two weeks, repeated two times.</li> <li>• Endpoints evaluated: Body weight, tumor volume, tumor weight, antitumor efficacy, tumor antiproliferative activity and tumor regression.</li> </ul> <p><b>Results:</b></p> <ul style="list-style-type: none"> <li>• Tumor volumes were significantly decreased in all test article treated animals compared to the control group.</li> <li>• At 2 and 20 mg/kg/day, %TGI was greater than 150%.</li> <li>• Schedule #1: KRN951 at 2 and 20 mg/kg/day sustained regression of the tumor and on the day after the final dose, the relative tumor volume weight (RVx) was less than 1 (0.64 and 0.23).</li> <li>• Schedule # 2 and Schedule #3 (had no dosing periods): tumor growth was reported during the periods when dosing was stopped but TGI were reported when dosing was started again.</li> <li>• On day 70 the control group had a relative tumor volume weight (RVx) of 7.15, in contrast all other dose groups with the different schedules had values of less than 1 (RVx 0.23 ~ 0.99).</li> </ul> <p><b>Conclusion:</b><br/>                 The Applicant concludes that doses of 2 and 20 mg/kg/day after a repeat dosing (up to 10 weeks) resulted in TGI. Even after a dosing rest period (2 weeks), tumor inhibition was reported once dosing was initiated for the next treatment cycle. The data suggest that no tolerance for KRN951 was developed. The data provided supported this conclusion.</p> | Group                              | Dose Amount | Dose Period | Mice | A | Media | 10 weeks | 8 | B | KRN951 2 mg / kg | 10 weeks | 8 | C | KRN951 20 mg / kg | 10 weeks | 8 | D | KRN951 2 mg / kg | 2 weeks dose + 2 weeks no dose x 3 | 8 | E | KRN951 20 mg / kg | 2 weeks dose + 2 weeks no dose x 3 | 8 | F | KRN951 2 mg / kg | 4 weeks dose + 2 weeks no dose x 2 | 8 | G | KRN951 20 mg / kg | 4 weeks dose + 2 weeks no dose x 2 | 8 |
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| Group                                          | Dose Amount                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | Dose Period                        | Mice        |             |      |   |       |          |   |   |                  |          |   |   |                   |          |   |   |                  |                                    |   |   |                   |                                    |   |   |                  |                                    |   |   |                   |                                    |   |
| A                                              | Media                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | 10 weeks                           | 8           |             |      |   |       |          |   |   |                  |          |   |   |                   |          |   |   |                  |                                    |   |   |                   |                                    |   |   |                  |                                    |   |   |                   |                                    |   |
| B                                              | KRN951 2 mg / kg                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | 10 weeks                           | 8           |             |      |   |       |          |   |   |                  |          |   |   |                   |          |   |   |                  |                                    |   |   |                   |                                    |   |   |                  |                                    |   |   |                   |                                    |   |
| C                                              | KRN951 20 mg / kg                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | 10 weeks                           | 8           |             |      |   |       |          |   |   |                  |          |   |   |                   |          |   |   |                  |                                    |   |   |                   |                                    |   |   |                  |                                    |   |   |                   |                                    |   |
| D                                              | KRN951 2 mg / kg                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | 2 weeks dose + 2 weeks no dose x 3 | 8           |             |      |   |       |          |   |   |                  |          |   |   |                   |          |   |   |                  |                                    |   |   |                   |                                    |   |   |                  |                                    |   |   |                   |                                    |   |
| E                                              | KRN951 20 mg / kg                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | 2 weeks dose + 2 weeks no dose x 3 | 8           |             |      |   |       |          |   |   |                  |          |   |   |                   |          |   |   |                  |                                    |   |   |                   |                                    |   |   |                  |                                    |   |   |                   |                                    |   |
| F                                              | KRN951 2 mg / kg                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | 4 weeks dose + 2 weeks no dose x 2 | 8           |             |      |   |       |          |   |   |                  |          |   |   |                   |          |   |   |                  |                                    |   |   |                   |                                    |   |   |                  |                                    |   |   |                   |                                    |   |
| G                                              | KRN951 20 mg / kg                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | 4 weeks dose + 2 weeks no dose x 2 | 8           |             |      |   |       |          |   |   |                  |          |   |   |                   |          |   |   |                  |                                    |   |   |                   |                                    |   |   |                  |                                    |   |   |                   |                                    |   |
| <p><b>Study #:</b><br/> <b>AV951-08046</b></p> | <p><b>Title:</b> AV-951: Antitumor Activity of AV-951 in Combination with Rapamycin in an Acquired AV-951-Resistant Murine Breast HER2 Tumor Xenograft Model<br/> <b>GLP:</b> No<br/> <b>Objectives:</b> To determine the effects of AV-951 alone and rapamycin alone and in combination on the BH504R3 murine breast HER2 tumor xenograft model.</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |                                    |             |             |      |   |       |          |   |   |                  |          |   |   |                   |          |   |   |                  |                                    |   |   |                   |                                    |   |   |                  |                                    |   |   |                   |                                    |   |

|                                                     | <p><b>Methods:</b></p> <ul style="list-style-type: none"> <li>Cell: BH504R3 mouse breast HER2 tumor cell line were injected subcutaneously in female NCr nu/nu mice</li> <li>Treatment: Once daily</li> </ul> <p><b>Study Design:</b></p> <table border="1" data-bbox="363 489 1448 730"> <thead> <tr> <th>Treatment</th> <th>Route</th> <th>Duration</th> <th>N</th> </tr> </thead> <tbody> <tr> <td>0.5% methylcellulose</td> <td>Oral</td> <td>16 days</td> <td>4</td> </tr> <tr> <td>AV-951 (5 mg/kg/day)</td> <td>Oral</td> <td>16 days</td> <td>9</td> </tr> <tr> <td>Rapamycin (0.5 mg/kg/day)</td> <td>Intraperitoneal (ip)</td> <td>16 days</td> <td>5</td> </tr> <tr> <td>AV-951 (5 mg/kg/day) Plus Rapamycin (0.5 mg/kg/day)</td> <td>Oral (AV-951) and ip (Rapamycin)</td> <td>16 days</td> <td>9</td> </tr> </tbody> </table> <ul style="list-style-type: none"> <li>Endpoints evaluated: Tumor growth inhibition was measured on Days 13, 18, 21 and 28.</li> </ul> <p><b>Results:</b></p> <ul style="list-style-type: none"> <li>Animals in the control group were sacrificed after 9 days because tumors reached IACUC limits of the testing facility.</li> <li>A dose of 5 mg/kg/day AV-951 resulted in tumor growth inhibition of 71%.</li> <li>A dose of 0.5 mg/kg/day rapamycin resulted in tumor growth inhibition of 44%.</li> <li>The combination of AV-951 (5 mg/kg/day) and Rapamycin (0.5 mg/kg/day) resulted in 100% TGI, relative to the control group.</li> </ul> <p><b>Conclusion:</b><br/>                 The Applicant concludes that the combined treatment showed the greatest tumor growth inhibition in the BH504R3 murine breast HER2 tumor xenograft model. The data provided supported this conclusion.</p> | Treatment | Route | Duration | N | 0.5% methylcellulose | Oral | 16 days | 4 | AV-951 (5 mg/kg/day) | Oral | 16 days | 9 | Rapamycin (0.5 mg/kg/day) | Intraperitoneal (ip) | 16 days | 5 | AV-951 (5 mg/kg/day) Plus Rapamycin (0.5 mg/kg/day) | Oral (AV-951) and ip (Rapamycin) | 16 days | 9 |
|-----------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------|-------|----------|---|----------------------|------|---------|---|----------------------|------|---------|---|---------------------------|----------------------|---------|---|-----------------------------------------------------|----------------------------------|---------|---|
| Treatment                                           | Route                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | Duration  | N     |          |   |                      |      |         |   |                      |      |         |   |                           |                      |         |   |                                                     |                                  |         |   |
| 0.5% methylcellulose                                | Oral                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | 16 days   | 4     |          |   |                      |      |         |   |                      |      |         |   |                           |                      |         |   |                                                     |                                  |         |   |
| AV-951 (5 mg/kg/day)                                | Oral                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | 16 days   | 9     |          |   |                      |      |         |   |                      |      |         |   |                           |                      |         |   |                                                     |                                  |         |   |
| Rapamycin (0.5 mg/kg/day)                           | Intraperitoneal (ip)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | 16 days   | 5     |          |   |                      |      |         |   |                      |      |         |   |                           |                      |         |   |                                                     |                                  |         |   |
| AV-951 (5 mg/kg/day) Plus Rapamycin (0.5 mg/kg/day) | Oral (AV-951) and ip (Rapamycin)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | 16 days   | 9     |          |   |                      |      |         |   |                      |      |         |   |                           |                      |         |   |                                                     |                                  |         |   |
| <p><b>Study #:</b><br/> <b>AV951-08011R</b></p>     | <p><b>Title:</b> Effect of AV-951 in Combination with Rapamycin on Tumor Growth in vivo: Genetically Engineered Breast HER2 Tumors</p> <p><b>GLP:</b> No</p> <p><b>Objectives:</b> To determine the effects of AV-951 alone and in combination with rapamycin on tumor growth, angiogenesis and proliferation on the BH469 murine breast HER2 tumor xenograft model.</p> <p><b>Methods:</b></p> <ul style="list-style-type: none"> <li>BH469 mouse breast HER2 tumor cell lines were injected subcutaneously in female NCr nu/nu mice.</li> <li>Treatment frequency: Once daily</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |           |       |          |   |                      |      |         |   |                      |      |         |   |                           |                      |         |   |                                                     |                                  |         |   |

| <b>Study Design:</b>                              |                                  |                        |          |
|---------------------------------------------------|----------------------------------|------------------------|----------|
| <b>Treatment</b>                                  | <b>Route</b>                     | <b>Duration (days)</b> | <b>N</b> |
| 0.5% methylcellulose                              | Oral                             | 42                     | 10       |
| AV-951 (5 mg/kg/day)                              | Oral                             | 42                     | 10       |
| Rapamycin (1 mg/kg/day)                           | Intraperitoneal (ip)             | 42                     | 10       |
| AV-951 (5 mg/kg/day) Plus Rapamycin (1 mg/kg/day) | Oral (AV-951) and ip (Rapamycin) | 42                     | 10       |

- Endpoints evaluated:  
 Following 5 days of dosing: tumor growth inhibition, tumor viability, angiogenesis and proliferation index.  
 Following 21 days of dosing: tumor growth inhibition.  
 Following 21 and 28 days of dosing: tumor viability, proliferation index and tumor resistance.

**Results:**

- After 5 or 28 days of dosing, mean tumor volume decreases were reported following treatment with rapamycin or AV-951. The greatest reduction was reported following the combined treatment.
- It was reported that in the AV-951 group, histopathology analysis showed that while the majority of the tumor cross-sections were necrotic, the tumor cell proliferation rate in the remaining viable areas remained high.
- The combined treatment group resulted in complete inhibition of tumor cell proliferation and with greater decrease in viable tumor areas.
- In the combined treatment group, the total proliferating tumor cells were significantly reduced in comparison to the single-compound treated groups.

**Conclusion:**  
 The Applicant concludes that the combined treatment showed the greatest tumor growth inhibition in the BH469 murine breast HER2 tumor xenograft model. The data provided supported this conclusion.

## 4.2 Safety Pharmacology

### Overall Summary:

A total of five safety pharmacology studies were performed, one *in vitro* hERG study, two *in vivo* cardiovascular studies in monkeys, one *in vivo* respiratory study in rats, and one central nervous system study in rats.

The *in vitro* hERG Tail Current study for tivozanib hydrochloride was designed with a single concentration. As such, a concentration response curve was not established (per ICHS7B), and the study provided no information regarding IC<sub>50</sub>. Accordingly, this was not considered a valid

study. An *in vivo* telemetry study was performed in male cynomolgus monkeys that received a single oral dose of KN951 (0.015, 0.3 or 3 mg/kg). A dose of 3 mg/kg resulted in increases in systolic, diastolic and mean arterial blood pressure 90 minutes post-dose. There were no test article-related effects on heart rates, RR, PR, QT, QTcF, QTcQ intervals and the QRS duration at any dose level. In an *in vivo* repeat-dose telemetry study (1 or 3 mg/kg/day for 28 or 14 days, respectively) in male cynomolgus monkeys, increases in systolic, diastolic and mean blood pressure were evident at 3 mg/kg/day. As such the single- and repeat-dose telemetry study findings in monkeys at 3 mg/kg were consistent. At doses  $\geq$  1 mg/kg/day in the monkey, decreases in heart rate, cardiac output, renal arterial blood flow and cardiac arterial blood flow were reported. A decrease in vascular relaxation response and decrease in sensitivity to acetylcholine were also reported at doses  $\geq$  1 mg/kg/day (HED 19 mg/day).

An *in vivo* respiration study in male rats receiving a single oral dose of tivozanib (0.3, 3, 30, and 400 mg/kg) showed no effects on respiration rate, tidal volume, neurobehavioral endpoints or physiological parameters (Irwin test).

- The *in vivo* cardiovascular system (monkey) NOAEL: 0.3 mg/kg/day (HED 5.8 mg/day).
- The *in vivo* central nervous system (rat) NOAEL: 0.3 mg/kg/day (HED 2.9 mg/day).
- The *in vivo* respiratory system (rat) NOAEL: 0.3 mg/kg/day (HED 2.9 mg/day).

|                                    |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
|------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Study #:</b><br><b>DRZZ1020</b> | <p><b>Title:</b> Effect of KRN951 on hERG Tail Current Recorded from Stably Transfected HEK293 Cells</p> <p><b>Conducting Laboratory:</b><br/> (b) (4)</p> <p><b>Date of study initiation:</b> 07 July, 2003<br/><b>GLP compliance:</b> Yes<br/><b>QA statement:</b> Yes<br/><b>Drug and lot #:</b> KRN951, CDM-001</p> <p><b>Objective and Methods</b><br/>The objective of this study was to examine the effect of the KRN951 (3 <math>\mu</math>g/mL) on the hERG tail current recorded from stably transfected HEK293 cells with hERG cDNA.</p> <p>KRN951 was tested at a single concentration. The concentration tested (3 <math>\mu</math>g/mL) was the maximum soluble concentration of KRN951 as determined in solubility testing. E-4031 (100 nM) was used as a positive control and tested in two cells of the vehicle and test article. The effect of KRN951 (3 <math>\mu</math>g/mL) was investigated in 5-6 cells and the vehicle (0.1% DMSO) was investigated in 5-6 cells.</p> |
|------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

|  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
|--|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|  | <p><b>Results</b></p> <ul style="list-style-type: none"> <li>• Analysis of formulation: The final concentration was determined to be 27.3% of the intended concentration (3 µg/mL). Therefore, a concentration of 0.82 µg/mL was the actual concentration of the solution applied to cells in the recording chamber.</li> <li>• The positive control at 100 nM inhibited hERG tail current by 88.8% (expected outcome).</li> <li>• KRN951 inhibited hERG tail current by 28% versus 18.9% at the control group. The difference was not statistically significant.</li> </ul> <p><b>Conclusion</b><br/>                 KRN951 at a concentration of 0.82 µg/mL, produced no inhibition of hERG tail current.</p> <p><b>Reviewer comment:</b></p> <ul style="list-style-type: none"> <li>• Only one concentration was tested (at maximum soluble concentration). Ascending concentrations should have been tested to establish a concentration response curve (per ICHS7B, section 3.1.2).</li> <li>• The final concentration used was 27.3% (0.82 µg/mL) of the nominal concentration and the concentration did not produce inhibition of hERG tail current.</li> <li>• Given the lack of concentration response curve this study provides no information regarding IC<sub>50</sub> and therefore the study was not considered to be valid.</li> </ul> |
|--|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

|                                                                 |                                                                                  |
|-----------------------------------------------------------------|----------------------------------------------------------------------------------|
| <b>Study title:</b> Effects of KRN951 in the Irwin Test in Rats |                                                                                  |
| Study no.:                                                      | DRZZ1017                                                                         |
| Sponsor:                                                        | Kirin Brewery Co., Ltd, 2-2 Soujya-Machi1 Chome, Maebashi, Gunma 371-0853, Japan |
| Conducting laboratory and location:                             | (b) (4)                                                                          |
| Date of study initiation:                                       | 09 April 2003                                                                    |
| GLP compliance and QA statement:                                | Yes                                                                              |
| Drug, lot #, and % purity:                                      | KRN951, CDM-001 and 98.8%                                                        |

**Key Findings:**

There were no test article-related effects reported on neurobehavioral endpoints and physiological parameters at all dose levels of KN951 (0.3, 3, 30 and 400 mg/kg) tested in the Irwin observation test (Irwin, 1968).

**Methods:**

NDA/BLA Multi-disciplinary Review and Evaluation {NDA 212904}  
 {FOTIVDA, tivozanib}

Doses/ Number/Sex/Group: KRN951 at 0.3, 3, 30, and 400 mg/kg; Chlorpromazine 20 mg/kg. N= 6/group  
 Route/Frequency of dosing: Oral gavage/Single dose  
 Dose volume: 10 mL/kg  
 Formulation/Vehicle : Vehicle, 0.5% methylcellulose  
 Sex/Species/Strain: Male Sprague-Dawley rats  
 Age: 7 weeks old  
 Weight: Body weights ranged from 185 to 232 g.  
 Positive control: Chlorpromazine  
 End points evaluated:
 

- Rats were observed at 2, 4, 8 and 24 hours post-dose. The parameters were scored on an arbitrary scale of '0-8'.
- The following parameters were monitored using Irwin primary observation test (Irwin, 1968):

|                    |                                                                                                                                                                                                                     |                                                                                                                                                                                                                                 |                                                                                                                                                                                                                                                                            |
|--------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Observation</b> | PA = Passivity<br>AG(Sp) = Abnormal gait (Spread limbs)<br>AC(Hu) = Abnormal carriage (Hunched)<br>↓LA = Decreased locomotor activity<br>↓F = Decreased fearfulness<br>↓GS = Decreased grip strength<br>PT = Ptosis | ↓TR = Decreased touch response<br>↓AL = Decreased alertness<br>↓ST = Decreased startle response<br>P = Piloerection<br>↓PN = Decreased pain response<br>↓BT = Decreased body tone<br>H = Hypothermia<br>CH = Chromodacryorrhoea | ↑U = Increased urination<br>V = Vocalization<br>DC = Dispersion in cage<br>↓PR = Decreased Pinna reflex<br>↓CR = Decreased corneal reflex<br>C = Catalepsy<br>L = Lacrimation<br>A = Apathy<br>DM = Dirty muzzle<br>N/A - not applicable - not tested at given time point. |
|--------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

*(excerpted from Applicant's report)*

Deviation from study protocol: None of the deviations affected the integrity or interpretability of the study.

**Results:**

- There were no test article-related findings reported on neurobehavioral endpoints and physiological parameters at all dose levels.
- The positive control group exhibited the expected effects.

**Conclusion:**

Male rats received a single oral dose of KN951 (0.3, 3, 30, and 400 mg/kg) and were tested in the Irwin observation test. There were no test article-related effects reported on neurobehavioral endpoints and physiological parameters at all doses assessed.

| <b>Study title:</b> Effects of KRN951 on Respiration Rate and Tidal Volume in Rats |                                                                                  |
|------------------------------------------------------------------------------------|----------------------------------------------------------------------------------|
| Study no.:                                                                         | DRZZ1018                                                                         |
| Sponsor:                                                                           | Kirin Brewery Co., Ltd, 2-2 Soujya-Machi1 Chome, Maebashi, Gunma 371-0853, Japan |
| Conducting laboratory and location:                                                | (b) (4)                                                                          |
| Date of study initiation:                                                          | 09 April 2003                                                                    |
| GLP compliance and QA statement:                                                   | Yes                                                                              |
| Drug, lot #, and % purity:                                                         | KRN951, CDM-001 and 98.8%                                                        |

**Key Findings:**

There were no test article-related effects reported on respiration rate or tidal volume in animals at 240 minutes and 24 hours post-dose, at any dose level tested.

**Methods:**

|                                |                                                                                                                                                                                                                                                                                                                                                                                                           |
|--------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Doses/ Number/Sex/Group:       | KRN951 at 0.3, 3, 30, and 400 mg/kg; Morphine HCl 20 mg/kg.<br>N= 6-8/group                                                                                                                                                                                                                                                                                                                               |
| Route/Frequency of dosing:     | Oral gavage/Single dose                                                                                                                                                                                                                                                                                                                                                                                   |
| Dose volume:                   | 10 mL/kg                                                                                                                                                                                                                                                                                                                                                                                                  |
| Formulation/Vehicle:           | Vehicle, 0.5% methylcellulose                                                                                                                                                                                                                                                                                                                                                                             |
| Sex/Species/Strain:            | Male Sprague-Dawley rats                                                                                                                                                                                                                                                                                                                                                                                  |
| Age/Weight:                    | 8 weeks old/ Body weights ranged from 236 to 295 g.                                                                                                                                                                                                                                                                                                                                                       |
| Positive control:              | Morphine HCl (intravenous injection)                                                                                                                                                                                                                                                                                                                                                                      |
| End points evaluated:          | <ul style="list-style-type: none"><li>• Conscious animals were restrained in body enclosed plethysmography chambers and respiratory parameters were recorded pre-dose (-10 minutes) and at approximately 240 minutes and 24 hours post-dose for test article and vehicle and -10, 60 and 240 minutes for the positive control.</li><li>• Respiration rate and tidal volume data were monitored.</li></ul> |
| Deviation from study protocol: | None of the deviations affected the integrity or interpretability of the study.                                                                                                                                                                                                                                                                                                                           |

**Results:**

- There were no test article-related effects on respiration rate and tidal volume of the conscious animals at any dose level.
- The positive control group exhibited the expected effects (decreases in respiration rate and tidal volume relative to pre-dose).

**Conclusion:**

Male rats received a single oral dose of KN951 (0.3, 3, 30, and 400 mg/kg) and were tested for effects on respiration rate and tidal volume. There were no test article-related findings

reported on respiration rate or tidal volume in animals after 240 minutes and 24 hours post-dose, at any dose level.

| <b>Study title:</b> Cardiovascular Effects of KRN951 in Conscious, Telemetered Cynomolgus Monkeys |                                                                                  |
|---------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------|
| Study no.:                                                                                        | DRZZ1019                                                                         |
| Sponsor:                                                                                          | Kirin Brewery Co., Ltd, 2-2 Soujya-Machi1 Chome, Maebashi, Gunma 371-0853, Japan |
| Conducting laboratory and location:                                                               | (b) (4)                                                                          |
| Date of study initiation:                                                                         | 11 February2003                                                                  |
| GLP compliance and QA statement:                                                                  | Yes                                                                              |
| Drug, lot #, and % purity:                                                                        | KRN951, CDM-001 and 98.8%                                                        |

**Key Findings:**

- At 3 mg/kg, significant increases in systolic (increases of 20%,16% and 5% at 90, 120 and 240 minutes post-dose, respectively), diastolic (increase of 21% at 90 minutes post-dose) and mean arterial blood pressure (increases of 19% and 18% at 90 and 120 minutes post-dose, respectively) were reported.
- There were no test article-related effects reported at any dose level in heart rates, RR, PR, QT, QTcF, QTcQ intervals and the QRS duration.

**Methods:**

Doses/ Number/Day of dosing: Latin square design:

| Animal Number | Day 1                 | Day 5                 | Day 8                 | Day 12                |
|---------------|-----------------------|-----------------------|-----------------------|-----------------------|
| 1             | Vehicle<br>1 ml/kg    | 3.0 mg/kg<br>KRN951   | 0.3 mg/kg<br>KRN951   | 0.015 mg/kg<br>KRN951 |
| 2             | 0.015 mg/kg<br>KRN951 | Vehicle<br>1 ml/kg    | 3.0 mg/kg<br>KRN951   | 0.3 mg/kg<br>KRN951   |
| 3             | 0.3 mg/kg<br>KRN951   | 0.015 mg/kg<br>KRN951 | Vehicle<br>1 ml/kg    | 3.0 mg/kg<br>KRN951   |
| 4             | 3.0 mg/kg<br>KRN951   | 0.3 mg/kg<br>KRN951   | 0.015 mg/kg<br>KRN951 | Vehicle<br>1 ml/kg    |

*(excerpted from Applicant's report)*

Route/Frequency of dosing: Oral gavage/Single dose  
 Dose volume: 1 mL/kg  
 Formulation/Vehicle: Vehicle, 0.5% methylcellulose  
 Sex/Species/Strain: Male cynomolgus monkeys  
 Age: 3 years and 11 months to 5 years and 1 month old  
 Device used: Animals were implanted with telemetry devices  
 Endpoints evaluated:
 

- Data was collected at least 30 minutes before dosing and ended approximately 6 hours post-dose.
- Measurements of systolic blood pressure (SBP), diastolic blood pressure (DBP), heart rate (HR) and the lead II ECG variables (measuring PR interval, RR interval, QRS duration and QT interval) were acquired continuously before and after dosing.
- Mean arterial blood pressure (MAP), QTcF and QTcQ.
- A visual inspection of all of the acquired ECG waveforms was performed for all monkeys following administration of vehicle and 3.0 mg/kg KRN951.

 Deviation from study protocol: None of the deviations affected the integrity or interpretability of the study.

**Results:**

- No clinical observations were reported at any dose level.
- At 3 mg/kg, significant increases in systolic (increases of 20%,16% and 5% at 90, 120 and 240 minutes post-dose, respectively), diastolic (increase of 21% at 90 minutes post-dose) and mean arterial blood pressure (increases of 19% and 18% at 90 and 120 minutes post-dose, respectively) were reported.
- There were no test article-related effects reported at any dose level in heart rates, RR, PR, QT, QTcF, QTcQ intervals and the QRS duration.

**Conclusion:**

Male cynomolgus monkeys received a single oral dose of KN951 (0.015, 0.3 or 3 mg/kg). A single dose of 3 mg/kg resulted in increases in systolic, diastolic and mean arterial blood pressure. There were no test article-related effects on heart rates, RR, PR, QT, QTcF, QTcQ intervals and the QRS duration at any dose level.

| <b>Study title:</b> KRN951 Multiple Oral Dosing in Crab Eating Monkeys (Cynomolgus monkey) Toxicity Study |                                                                                                                                                   |
|-----------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------|
| Study no.:                                                                                                | 4655                                                                                                                                              |
| Objective:                                                                                                | To examine the effect of a 2 or 4 week multiple oral dosing regimen of KRN951 on the heart beat pulse rate and blood flow of crab eating monkeys. |
| Sponsor:                                                                                                  | Pharmaceutical Development Laboratories<br>Kirin Brewery Co., Ltd.<br>Maebashi-shi, Gunma 528-0853                                                |
| Conducting laboratory and location:                                                                       | (b) (4)                                                                                                                                           |
| GLP compliance and QA statement:                                                                          | Yes according to Japan GLPs                                                                                                                       |
| Drug, lot #, and % purity:                                                                                | KRN951, CDM-001 and 98.8%                                                                                                                         |

**Key Findings:**

- At 3 mg/kg/day (HED 58 mg/day), there were test article-related increases in systolic, diastolic and mean blood pressure by up to 28%, 22% and 28% during the dosing period (days 1 to 14), respectively.
- At 1 mg/kg/day, there were no test article-related effects on systolic, diastolic and mean blood pressure.
- At 1 and 3 mg/kg/day, there were test article-related decreases in heart rate by up to 44% and 35%, respectively, during the dosing period (animals at 3 and 1 mg/kg/day were dosed for 14 or 28 days, respectively).
- Decreases of 34% and 38% in cardiac output were reported at 1 and 3 mg/kg/day, respectively. A decrease in renal arterial blood flow was evident at 1 (-67%) and 3 mg/kg/day (-65%) and a decrease in cardiac arterial blood flow was evident at 1 (-59%) and 3 mg/kg/day (-46%).
- Test article-related decrease in vascular relaxation response was observed at doses  $\geq$  1 mg/kg/day (HED 19 mg/day). The EC<sub>50</sub> (-log M) value for ACh was lower at 1 mg/kg/day (7.12) and 3 mg/kg/day (6.84) than the control group (7.19).

**Methods:**

NDA/BLA Multi-disciplinary Review and Evaluation {NDA 212904}  
 {FOTIVDA, tivozanib}

Doses/ Number/Day  
 of dosing:

| Study Group   | Dose Amount<br>(mg/kg/day) | Animals Used<br>(Animal ID Number) | Dose Period |
|---------------|----------------------------|------------------------------------|-------------|
| Control Group | 0                          | 3 (1101 □ 1103)                    | 28 days     |
| KRN951        | 1                          | 3 (1201 □ 1203)                    | 28 days     |
| KRN951        | 3                          | 3 (1301 □ 1303)                    | 14 days     |

□= to  
 (excerpted from Applicant's report)

Route/Frequency of  
 dosing:

Oral gavage/Daily

Dose volume:

10 mL/kg

Formulation/Vehicle:

Vehicle, 0.5% methylcellulose (MC)

Sex/Species/Strain:

Male cynomolgus monkeys

Age:

2 to 3 years old

Device used:

Animals were implanted with telemetry devices

Endpoints evaluated:

- Daily observations (twice/day) during the dosing period.
- Body weights were measured on Day 1 and weekly thereafter.
- Systolic blood pressure, diastolic blood pressure, average blood pressure and heart beat rate were measured 3 days prior to first dose and daily during the dosing period. In the 1 mg/kg/day group, measurements were taken starting on day 14.
- Blood pressure was measured for 1.5 hours prior to dose administration and for 4.5 hours post-dose.
- Blood sample was taken once every three or four days to assess blood plasma for renin activation and Creatine phosphokinase (CPK).
- At the end of dosing cardiac output, carotid artery blood flow volume and renal artery blood flow volume were measured.
- Vascular endothelial function was performed by measuring an endothelium-dependent, nitric oxide-mediated vasodilatory response (ACh-induced) from extract samples taken from the right carotid artery. In one experiment, Acetylcholine (ACh) was added to the samples at concentrations ranging from  $10^{-9}$ M to  $10^{-6}$ M, followed by Papaverine at  $10^{-4}$ M, to achieve a maximum relaxation effect (baseline). In a second experiment, a nitric oxide inhibitor, L-NAME,  $3 \times 10^{-5}$  M was added to samples treated with ACh at concentrations ranging from  $10^{-9}$ M to  $10^{-6}$ M, and Papaverine at  $10^{-4}$ M. The relaxation percentage at each ACh concentration was calculated against the baseline (100%)
- Ophthalmological examinations was performed.

Deviation from study  
 protocol:

None of the deviations affected the integrity or interpretability of the study.

**Results:**

- At 3 mg/kg/day, there were test article-related increases in systolic, diastolic and mean blood pressure by up to 28%, 22% and 28% during the dosing period (day 1 to 14), respectively. This data is in agreement with the findings reported in prior cardiovascular study (#DRZZ1019), in which produced increases in systolic, diastolic and mean blood pressure by up to 20%, 21% and 19%, respectively.
- At 1 mg/kg/day, there were no test article-related effects on systolic, diastolic and mean blood pressure.

**Percent Change from Control at 3 mg/kg/day:**

| Days                       | 3   | 4   | 5   | 6   | 7   | 10   | 13   | 14  |
|----------------------------|-----|-----|-----|-----|-----|------|------|-----|
| <b>Systolic</b>            | 19* | 20* | 27* | 28* | 23* | 19** | 21** | 28* |
| <b>Diastolic</b>           | 18  | 22* | 29  | 26  | 26  | 24   | 22*  | 27  |
| <b>Mean blood pressure</b> | 18* | 21* | 28* | 26* | 24* | 21*  | 20*  | 27* |

\* statistically significant

**Reviewer comment:**

*In contrast to the Applicant's conclusion stating the minor rise after dosing in systolic, diastolic and mean blood pressure was not of a large enough magnitude to be considered a test article-related, this reviewer concludes that the observed increases in systolic, diastolic and mean blood pressure at 3 mg/kg/day were of sufficient magnitude to be considered a safety signal and test article-related. In addition, these results are in agreement with the findings reported in a prior cardiovascular study (#DRZZ1019), in which the test article produced increases in systolic, diastolic and mean blood pressure by up to 20%, 21% and 19%, respectively. The Applicant based their conclusion on standards established in the protocol, where an effect was considered only if there was a rise of more than 15 mm Hg at the end of dosing (3 day period), as compared to the average value of the 3 day period before the start of dosing. But using the control group for comparison the magnitudes are large enough to be test article-related.*

- At 1 and 3 mg/kg/day, there were test article-related decreases in heart rate by up to 44% and 35%, respectively, during the dosing period.

**Percent change at 3 and 1 mg/kg/day from control:**

|                         |           |           |           |           |           |           |           |           |           |           |           |           |           |           |
|-------------------------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|
| <b>Days</b>             | <b>1</b>  | <b>2</b>  | <b>3</b>  | <b>4</b>  | <b>5</b>  | <b>6</b>  | <b>7</b>  | <b>8</b>  | <b>9</b>  | <b>10</b> | <b>11</b> | <b>12</b> | <b>13</b> | <b>14</b> |
| <b>HR (3 mg/kg/day)</b> | -8        | -23*      | -26       | -18       | -20       | -30       | -11       | -35       | -35       | -22       | -18       | -28       | -21       | -27       |
| <b>Days</b>             | <b>15</b> | <b>16</b> | <b>17</b> | <b>18</b> | <b>19</b> | <b>20</b> | <b>21</b> | <b>22</b> | <b>23</b> | <b>24</b> | <b>25</b> | <b>26</b> | <b>27</b> | <b>28</b> |
| <b>HR (1 mg/kg/day)</b> | -34       | -37*      | -33       | -39       | -44       | -33       | -31       | -35       | -32       | -43       | -42*      | -38       | -33       | -33       |

Negative sign (-) = decrease; HR = heart rate; \* statistically significant

- Decreases of 34% and 38% in cardiac output were reported at 1 and 3 mg/kg/day, respectively. A decrease in renal arterial blood flow was evident at 1 and 3 mg/kg/day.

The decrease at the 3 mg/kg/day was statistically significant (-65%), while the decrease at 1 mg/kg/day was not. The decrease at 1 mg/kg/day was considered to be biologically significant due to the magnitude of effect (-67%). A decrease in cardiac arterial blood flow was evident at 1 and 3 mg/kg/day. The decrease at 1 mg/kg/day was statistically significant (-59%), while the decrease at 3 mg/kg/day was not. However, the decrease at 3 mg/kg/day was considered to be biologically significant due to the magnitude of effect (-46%).

Table 4 Cardiac output, carotid and renal arterial blood flow in male monkeys administered KRN951 orally for 14 or 28 days

| Group                 | Duration of administration (days) | No. of animals | Cardiac output (mL/min) | Carotid arterial blood flow (mL/min) | Renal arterial blood flow (mL/min) |
|-----------------------|-----------------------------------|----------------|-------------------------|--------------------------------------|------------------------------------|
| Control <sup>a)</sup> | 28                                | 3              | 222<br>±37              | 22<br>±4                             | 23.5<br>±7.6                       |
| KRN951<br>1 mg/kg/day | 28                                | 3              | 146*<br>±29             | 9*<br>±5                             | 7.8<br>±6.9                        |
| KRN951<br>3 mg/kg/day | 14                                | 3              | 138*<br>±23             | 12<br>±9                             | 8.3*<br>±3.1                       |

Each value represents the mean±S.D.

a) : Control animals were administered 0.5% methyl cellulose solution orally.

Significant difference from control vs. KRN951 1 mg/kg, \* : p<0.05 (Student's t-test).

Significant difference from control vs. KRN951 3 mg/kg, \* : p<0.05 (Student's t-test).

(excerpted from Applicant's report)

*Reviewer's comments:*

- In contrast to the Applicant's conclusion stating that there were no effects on cardiac output observed at any dose level, this reviewer concludes that a decrease in cardiac output was evident at 1 and 3 mg/kg/day. The decrease in cardiac output agrees with the decrease in heart rate reported at both dose levels.

- In contrast to the Applicant's conclusion stating that no effects were observed in renal arterial blood flow, this reviewer concluded that a decrease in renal arterial blood flow was evident at 1 and 3 mg/kg/day. The decrease at 3 mg/kg/day was statistically significant, while the decrease at 1 mg/kg/day was not. However, the decrease at 1 mg/kg/day was considered to be biologically significant due to the magnitude of effect (-67%).

- In contrast to the Applicant's conclusion stating that no effects were observed in cardiac arterial blood flow, this reviewer concluded that a decrease in cardiac

*arterial blood flow was evident at 1 and 3 mg/kg/day. The decrease at 1 mg/kg/day was statistically significant, while the decrease at 3 mg/kg/day was not. The decrease at 3 mg/kg/day was considered to be biologically significant due to the magnitude of effect (-46%).*

- There were no test article-related effects on rennin and CPK values.
- There was a test article-related decrease in the ACh-induced vascular relaxation response (% relaxation rate) at 3 mg/kg/day KRN951, at all ACh concentrations assessed. This effect was suppressed when L-NAME was added to samples, thus indicating that the potential mechanism of blood pressure change may be due to an inhibitory effect on vascular endothelial-derived nitric oxide production, causing a rise in peripheral vascular resistance and blood pressure

### **Conclusion:**

Cynomolgus monkey dosed with KRN951 at 1 or 3 mg/kg/day for 28 or 14 days, respectively. At 3 mg/kg/day (HED 58 mg/day), increases in systolic, diastolic and mean blood pressure were evident. At doses  $\geq 1$  mg/kg/day, decreases in heart rate, cardiac output, renal arterial blood flow and in cardiac arterial blood flow were evident. A decrease in vascular relaxation response was evident at doses  $\geq 1$  mg/kg/day (HED 19 mg/day).

## **5 Pharmacokinetics/ADME/Toxicokinetics**

### **Overall Summary:**

Tivozanib TK profile following oral administration was approximately linear in mice, rats and monkeys, with  $C_{max}$  and AUC increasing in an approximately dose proportional manner. No significant gender differences in exposure were reported. The rate of absorption was moderate and unaffected by dose level or duration of treatment in rats and monkeys, while, the rate of absorption ( $T_{max}$ ) and elimination half-life ( $t_{1/2}$ ) were different between species.

In *in vitro* distribution studies conducted using animal or human plasma, it was shown that the test article bound to plasma proteins at  $> 97.6\%$ , and protein binding was predominantly to albumin, with low binding to  $\alpha$ -1-acid glycoprotein. KRN951 mainly partitioned into the plasma/serum component of blood.

Quantitative data on the tissue distribution of test article-related radioactivity in whole body of rats showed that the distribution of radioactivity was maximal at 4 hours post-dose. The highest radioactivity tissue concentrations were measured in the preputial gland, harderian gland, white fat and the liver. The concentrations in both the ovary and uterus were similar to the blood levels, and those in testes were significantly less than in the blood. The majority of the radiation was eliminated from tissues at 24 hours post-dose, and by 72 hours post-dose the radiations levels were below the limit of quantification. In pigmented rats, melanin binding to

the choroid layer of the eye was apparent and levels decreased steadily over 120 hours post-dose.

*In vitro* and *in vivo* metabolism studies with KRN951 were performed and showed that in serum, the parent compound (KRN951) was the predominant circulating component (91% and 78% of the total radioactivity exposure in rat and monkey serum, respectively) with the metabolites M4 (mono-oxidation)/M5 (*N*-oxide of tivozanib) co-eluting and M63 in rats only. The parent compound was not detected in the urine, and metabolites detected in urine represented less than 0.5% of the administered radioactive dose. In feces, the parent compound was the main component and other metabolites detected represented less than 5% of the administered radioactive dose. *In vitro* metabolism studies showed that KRN951 metabolism was low in all species studied, as was evident by the low hepatic clearance, and that KRN951 appeared to be metabolized mainly by oxidation and demethylation. All prominent human metabolites (M1 through M24) were present in both rat and monkey with the exception of M11 (glucuronide), which was unique to human hepatocytes (minor >0.5%) and M10 which was not observed with rat hepatocytes. M14 was present at >10% of total radioactivity and was designated as a major metabolite in human, monkey and rat. The metabolic profile of the monkey was the closest to human, followed by the rat. Comparison of the metabolic profile of tivozanib in human, monkey, dog and rat liver microsomes showed that monkey is the closest to human followed by the rat and dog is the most different. CYP3A4 and CYP1A1 are the major human hepatic CYP isoform involved in the metabolism of tivozanib.

In rats and monkeys the main excretion route was through the feces, and to a smaller extent (2-3%) through urine.

Overall the data supported the use of rats and monkey in nonclinical studies, as these species would be expected to provide adequate coverage for potential human metabolites and associated toxicities.

#### ***Individual Summaries:***

#### ***Absorption studies:***

- *The toxicokinetics (TK) data supporting 10 toxicology studies was compromised due to data integrity issues and therefore are in non-compliance with the GLP regulations. The following reports were amended and data was discarded: 6691-158 (DRZZ1047), RCK0003, RZZ1008, RZZ1009, RZZ1010, RZZ1011, RZZ1012, RZZ1013, RZZ1014, and RZZ1015. As such, the data from these studies cannot be used to support this application, and were not reviewed.*
- The remaining absorption data is discussed in detail in the toxicology sections of this NDA review, since these data were generated as part of the nonclinical toxicology studies.
- The following tables summarize the key PK parameters from a single dose studies in Nude mice (AV951-08028) and rats (PKP0227):

**Mean pharmacokinetic parameters following a single oral administration to female Nude mice**

| Dose (mg/kg) | C <sub>max</sub> (ng/mL) | T <sub>max</sub> (hr) | AUC (hr·ng/mL) <sup>a</sup> | t <sub>1/2</sub> (hr) |
|--------------|--------------------------|-----------------------|-----------------------------|-----------------------|
| 0.04         | 21.6 ± 1.7               | 3.63 ± 0.75           | 339 ± 75                    | 9.25 ± 1.69           |
| 0.2          | 108 ± 15                 | 2.63 ± 0.95           | 1640 ± 250                  | 7.78 ± 0.53           |
| 1            | 484 ± 60                 | 4.25 ± 2.87           | 7640 ± 830                  | 8.13 ± 1.86           |
| 5            | 2823 ± 479               | 3.50 ± 3.00           | 44500 ± 3600                | 7.94 ± 0.62           |

(excerpted from Applicant's report)

**Mean pharmacokinetic parameters following a single oral administration to female Nude mice**

| Dose (mg/kg) | C <sub>max</sub> <sup>a</sup> (ng/mL) | T <sub>max</sub> (hr) | AUC <sub>0-∞</sub> (hr·ng/mL) <sup>a</sup> | t <sub>1/2</sub> (hr) |
|--------------|---------------------------------------|-----------------------|--------------------------------------------|-----------------------|
| 5            | 1361                                  | 2                     | 11513                                      | 6.11                  |
| 20           | 7708                                  | 2                     | 68233                                      | 4.58                  |

(excerpted from Applicant's report)

- The following table summarizes the key TK parameters for the 26-week rat study (1458-005), and the 13-week (1458-006) and 39-week (6691-159) monkey studies:

| Study Number                   | 1458-005           |                   |                   | 1458-006           |              |              | 6691-159           |           |             |            |            |
|--------------------------------|--------------------|-------------------|-------------------|--------------------|--------------|--------------|--------------------|-----------|-------------|------------|------------|
| Species                        | CD rats            |                   |                   | Cynomolgus monkeys |              |              | Cynomolgus monkeys |           |             |            |            |
| Dose (mg/kg/day):              | 0.005 <sup>c</sup> | 0.02 <sup>c</sup> | 0.08 <sup>c</sup> | 0.01               | 0.03         | 0.1          | 0.01               | 0.03      | 0.1         | 0.3        | 1.0        |
| Day of study                   | D91                | D91               | D91               | D91                | D91          | D91          | D28                | D28       | D28         | D28        | D28        |
| AUC <sub>0-24</sub> (hr·ng/mL) | 264                | 872               | 3610              | 62.4 ± 11.1        | 192 ± 35.6   | 685 ± 192    | 65.1 ± 7.0         | 104 ± 11  | 793 ± 186   | 1531 ± 542 | 4127 ± 966 |
| t <sub>1/2</sub> (hr)          | 38.7               | 16.4              | 28.4              | 9.56 ± 2.00        | 10.4 ± 2.07  | 12.4 ± 5.65  | 7.7 ± 1.3          | 8.2 ± 1.4 | 8.2 ± 2.1   | 8.3 ± 1.3  | 9.2 ± 0.6  |
| C <sub>max</sub> (ng/mL)       | 15.0               | 56.9              | 229               | 4.77 ± 0.812       | 14.5 ± 2.78  | 50.7 ± 16.3  | 5.4 ± 1.3          | 8.5 ± 1.4 | 60.9 ± 14.7 | 112 ± 37   | 258 ± 62   |
| T <sub>max</sub> (hr)          | 3                  | 3                 | 4                 | 2.60 ± 0.966       | 2.10 ± 0.738 | 2.40 ± 0.843 | 3.7 ± 0.8          | 3.7 ± 0.8 | 4.0 ± 0.0   | 4.0 ± 0.0  | 6.4 ± 6.3  |

(excerpted from Applicant's report)

**Excretion studies:**

- In rats administered an oral or IV dose of [<sup>14</sup>C] KRN951, the majority of the test article was excreted in feces (91%) by 72 hours post-dose, suggesting that the main excretion

route of the test article was through the feces. A limited amount of radioactivity (< 2%) was excreted into the urine (not the parent compound).

- Data generated from the bile duct-cannulated rats, suggested that [<sup>14</sup>C]KRN951 is also excreted through the bile (up to 37% of the total radioactivity). Another non-biliary route of excretion of tivozanib and/or its metabolites from the systemic circulation was the gastrointestinal tract which showed approximately 40% of the radioactivity.
- In monkeys, after an oral dose of [<sup>14</sup>C] KRN951, the radioactivity excreted in the urine and feces, were 3.40% and 27.4%, respectively, within 24 hours postdose. These data confirm that the main excretion route of the test article, through the feces, was indeed similar in the rat and monkey.

**Distribution studies:**

- In an *in vitro* study conducted using animal or human plasma, it was shown that the test article bound to plasma proteins of the rat (99.3%), human (99.7%) and monkey (97.6%), with no apparent gender differences.
- In human plasma, the protein binding was mainly to albumin, with low binding to  $\alpha$ -1-acid glycoprotein.
- *In vitro* studies conducted with human blood indicated that KRN951 was mainly partitioned into the plasma/serum component of blood. Similarly, the reported data from the rat study suggested limited association of KRN951 within red blood cells.
- Quantitative data on the tissue distribution of test article-related radioactivity in whole body of male and female albino and male pigmented rats showed that the distribution of radioactivity was similar between the genders and strains. The extent of the tissue penetrance was low, with tissue/blood ratios of less than 1 in the majority of tissues. Maximal tissue concentrations were observed at 4 hours post-dose. The highest radioactivity tissue concentrations were measured in the preputial gland, harderian gland, white fat and liver. The lowest radiation levels were in the spinal cord and brain. The concentrations in both the ovary and uterus were similar to the blood levels, and those in testes were significantly less than in the blood. In albino rats, the majority of the radiation was eliminated from tissues at 24 hours post-dose, and by 72 hours post-dose the radiations levels were below the limit of quantification. In pigmented rats, melanin binding to the choroid layer of the eye was apparent and levels decreased steadily over 120 hours post-dose.

**Metabolism studies:**

*In vitro* and *in vivo* metabolism studies with KRN951 were performed:

- The *in vivo* metabolic profiles were assessed in rat and monkey serum, urine and feces. In serum, the parent compound (KRN951) was the predominant circulating component (91% and 78% of the total radioactivity exposure in rat and monkey serum, respectively) with the metabolites M4 (mono-oxidation)/M5 (*N*-oxide of tivozanib) co-eluting and M63 in rats only. The parent compound was not detected in the urine, and none of the metabolites detected in urine represented an average of greater than 0.5% of the

administered radioactive dose. In feces, the parent compound was the main component and each of the other metabolites detected, M37/57 co-eluting, M42, and M7, represented an average of less than 1% and < 4.99% in monkey and rat, respectively. KRN951 was not detected in rat bile, but the metabolites were evident at approximately 0.388% of the administered radioactive dose.

- *In vitro* metabolism studies showed that KRN951 metabolism was low in all species studied (rats, dogs, cynomolgus monkeys, and humans), as was evident by the low hepatic clearance (< 25% of blood flow). KRN951 appeared to be metabolized by oxidation, demethylation, glucuronidation, sulfation, or a combination of these pathways.
- Twenty-two different metabolites (M1-M24) were detected in rat, monkey and human hepatocyte incubations with AV-951 with the exception of M11 (glucuronide), which was unique to human hepatocytes (minor >0.5%) and M10, which was not observed with rat hepatocytes. M14 (desmethyl glucuronide) was present at >10% of total radioactivity and was designated as a major metabolite in human, monkey and rat.
- Comparison of the metabolic profile of KRN951 in human, primate, dog and rat liver microsomes showed that the metabolic profile of the monkey was the closest to human, followed by the rat and dog. Metabolites formed by rat, dog and monkey were the same as those produced in human liver microsomes with the exception of one metabolite in monkey which eluted earlier than any of the four metabolites observed in the other species. Overall the data supported the use of rats and monkey in nonclinical studies, as these species would provide adequate coverage for potential human metabolites and potential associated toxicities.
- CYP3A4 and CYP1A1 were the major human hepatic CYP isoform involved in the metabolism of KRN951.
- Substantial levels of <sup>14</sup>C-KRN951 desmethyl glucuronide metabolites were formed by UGT isoenzymes. Metabolite M14, a desmethyl glucuronide metabolite, was the major metabolite formed by six UGT enzymes. Other observed glucuronide metabolites were M10 and M25. Since the major metabolite (M14) was formed by six different UGT isoenzymes, inhibition of any one of these enzymes is not likely to cause substantial drug-drug interactions.
- KRN951 inhibited glucuronidation of UGT substrates 4-MU and p-NP to a small extent. Therefore, tivozanib is not a potent inhibitor of UGT activities.

## 5.1 PK/ADME

### Studies Conducted:

|                             |                                                                                                                                                                                                                                                                                                                                                                             |
|-----------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Study #:</b><br>DRZZ1028 | <b>Title:</b> The Disposition of Total Radioactivity in the Rat Following Single Oral and Single Intravenous Administration of [ <sup>14</sup> C] KRN951<br><b>GLP:</b> Yes<br><b>Objectives:</b> To evaluate the excretion of total radioactivity into urine, feces and expired air following a single oral and a single IV administration of [ <sup>14</sup> C]-tivozanib |
|-----------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

hydrochloride to male rats. In addition, this study evaluated the PK and distribution of tivozanib hydrochloride to red blood cells.

**Methods:**

Male (treated orally and intravenously (IV)) and female (treated IV) rats were treated based on the schedule listed in the table (below) and were housed in individual glass metabolism cages. Urine, feces and expired air were collected:

**Study design:** This study was conducted in five phases.

| Phase | Investigation       | Route       | Number of animals<br>male (female) | Target Dose Level<br>(mg/kg) | Sample collection                                                 |
|-------|---------------------|-------------|------------------------------------|------------------------------|-------------------------------------------------------------------|
| 1     | Excretion           | Oral        | 3                                  | 1                            | Urine <sup>a</sup> , feces <sup>a</sup><br>Expired air: 48, 96 hr |
| 2     | Excretion           | Intravenous | 4                                  | 0.5                          | Urine <sup>a</sup> , feces <sup>a</sup><br>Expired air: 48, 96 hr |
| 3     | PK                  | Oral        | 3(3)                               | 1                            | Blood (plasma) <sup>b</sup>                                       |
| 4     | PK                  | Intravenous | 3(3)                               | 0.5                          | Blood (plasma) <sup>b</sup>                                       |
| 5     | Blood cell transfer | Oral        | 3                                  | 1                            | Blood<br>(4, 24, 72, 120 hr post-dose)                            |

a : Collected at selected time points through 168 hours post-dose

b: Collected at selected time points through 120 hours post-dose  
 (excerpted from Applicant's report)

**Results:**

- The concentrations of radioactivity in the expired air trap were below the limit of quantification at all collection time points.
- Following oral administration in male rats, the majority of the test article was excreted in feces and urine by 72 hours post-dose as was evident by the total radioactivity recovered (87.8% and 1.70%, respectively).
- IV administration of the test article to male and female rats resulted in similar outcome to the oral administration, suggesting that the main excretion route of the test article is fecal excretion.
- At the end of the collection period (168 hours postdose) for male and female rats, a mean total of 95.7% and 93.9% of the dose was recovered in urine, feces, cage wash, expired air traps and carcass following oral and IV administration, respectively.
- Limited association of radioactivity with red blood cells was suggested based on the data that following oral dose of the test article, the transfer of total radioactivity to red blood cells was evident at the later time points when radioactivity concentrations were low and the blood cell transfer ratios increased with time.
- Following oral dose the mean C<sub>max</sub> and AUC were 1764 ng equiv/mL and 2279 ng equiv/mL and 29243 and 38732 ng equiv.h/mL for male and female rats, respectively.
- Following IV administration, mean AUC<sub>inf</sub> values were 26019 and 29933 ng equiv.h/mL in male and female rats, respectively.

|                                            |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
|--------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                            | <p><b>Conclusion:</b><br/>                 In rats administered an oral or IV dose of [<sup>14</sup>C] KRN951, the majority of test article was excreted in feces by 72 hours post-dose, indicating that the main excretion route of the test article is fecal excretion.</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
| <p><b>Study #:</b><br/> <b>Pk0403</b></p>  | <p><b>Title:</b> Pharmacokinetic Study of AV951 – Biliary Excretion of [<sup>14</sup>C] AV951 in Rats<br/> <b>GLP:</b> No<br/> <b>Objectives:</b><br/>                 To evaluate the amount of [<sup>14</sup>C]KRN951 eliminated through the bile, after a single intravenous administration, by measuring the amount of radioactivity in the urine, feces and bile.</p> <p><b>Methods:</b><br/>                 Bile duct cannulated male rats were dosed intravenously once at 0.5 mg/kg with [<sup>14</sup>C]KRN951 and radioactivity in urine and feces and bile were measured up to 72 hours post-dose.</p> <p><b>Results:</b><br/>                 At seventy two hours post-dose, greater than 80% of the radiation was excreted, with the percentage of excretion into the feces (via gastrointestinal tract) and bile being about the same at 39.8% and 36.6%, respectively and less than 5% excreted in urine.</p> <p><b>Conclusion:</b><br/>                 The data suggested that in rats, [<sup>14</sup>C]KRN951 was excreted through the bile and feces.</p> |
| <p><b>Study #:</b><br/> <b>8255110</b></p> | <p><b>Title:</b> Metabolism of <sup>14</sup>C-Tivozanib Following Oral Administration to Rats<br/> <b>GLP:</b> Yes<br/> <b>Objectives:</b> The purpose of this study was to profile and identify the metabolites of <sup>14</sup>C-tivozanib following oral administration to rats.</p> <p><b>Methods:</b><br/>                 Eleven male bile duct-intact Sprague Dawley rats and two bile duct-cannulated (BDC) male rats were used.</p> <p><b>Study design:</b></p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |

| Group | Number of Male Animals | Dose Route | Target Dose Level (mg/kg) | Target Dose Volume (mL/kg) | Samples Collected      |
|-------|------------------------|------------|---------------------------|----------------------------|------------------------|
| 1     | 9                      | Oral       | 5                         | 10                         | Blood                  |
| 2     | 2                      | Oral       | 5                         | 10                         | Urine and Feces        |
| 3     | 2 BDC                  | Oral       | 5                         | 10                         | Urine, Feces, and Bile |

**BDC** Bile duct-cannulated.

**Notes:** The radioactive dose was approximately 200 µCi/kg.

*(excerpted from Applicant's report)*

- Rats were dosed orally with 5 mg/kg (~200 µCi/kg) [<sup>14</sup>C]-tivozanib hydrochloride.
- Urine, feces and blood were collected during the pre-dose period through 24 hours post-dose to measure concentration of radioactivity.

**Results:**

- An average of 1.26%, 22% and 53.7% of the administered [<sup>14</sup>C]-tivozanib hydrochloride dose was eliminated in the urine, bile and feces, respectively, indicating that the main route of excretion is through the digestive system (feces).
- Tivozanib (parent compound) was not detected in urine and bile, but the metabolites were evident at approximately 0.5% and 0.388% of the administered radioactive dose, respectively. While in feces, parent compound was the predominant radioactive component (representing 32.2 and 33.3% of the administered radioactive dose in intact and bile duct-cannulated rats, respectively). The main metabolites detected (M7, M42, M37/M57) represented < 4.99% of the administered radioactive dose.
- The parent compound was the major circulating component in serum, representing approximately 91% of the total radioactivity exposure in serum, along with metabolites M4 (mono-oxidation)/M5 (N-oxide of tivozanib)/M63 (reduction of the isoxazole ring of tivozanib) co-eluting, which represented approximately 9% of the total radioactivity exposure in serum.
- In bile, the main metabolites detected were M55 (glutathione conjugation)/M56 (N-oxidation couple with glutathione conjugation followed by cleavage of the conjugate) co-eluting, and M15 (mono-oxidation coupled with glucuronidation)/M60 (O-demethylation coupled with sulfation; co-eluting), representing 6.42 and 8.22% of the administered radioactive dose, respectively. Each of the other unknown metabolites detected in bile represented less than 1.5% of the administered radioactive dose.
- C<sub>max</sub> and AUC for tivozanib were 8560 ng equiv [<sup>14</sup>C]-tivozanib /g and 125000 ng equiv [<sup>14</sup>C]-tivozanib. hour/g

|                                            | <p><b>Conclusion:</b><br/>                 Tivozanib (parent compound) was the major circulating component representing approximately 91% of the total radioactivity exposure in rat serum. Tivozanib was not detected in urine and bile but the metabolites were evident at approximately 0.5% and 0.388% of the administered radioactive dose. While in feces, tivozanib was the predominant radioactive component and the main metabolites detected (M7, M42, M37/M57) represented &lt; 4.99% of the administered radioactive dose.</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |            |                           |                            |                           |                            |                   |   |   |      |   |   |                         |
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| <p><b>Study #:</b><br/> <b>8255111</b></p> | <p><b>Title:</b> Metabolism of <sup>14</sup>C-Tivozanib Following Oral Administration to Monkeys<br/> <b>GLP:</b> Yes<br/> <b>Objectives:</b> The purpose of this study was to profile and identify the metabolites of <sup>14</sup>C-tivozanib following oral administration to monkeys.</p> <p><b>Methods:</b></p> <ul style="list-style-type: none"> <li>• Two male Cynomolgus monkeys were used on study.</li> <li>• Following a single oral dosing (<sup>14</sup>C-tivozanib), blood, urine and feces were collected pre-dose and up to 24 hours post-dose.</li> <li>• Aliquots of urine supernatants, and the serum and fecal extracts were analyzed by HPLC, with fractions collected and analyzed by TopCount solid scintillation counting.</li> <li>• LC-MS techniques were used to determine the metabolite composition in urine, feces, and serum samples.</li> </ul> <p><b>Study design:</b></p> <table border="1" data-bbox="386 1241 1393 1352"> <thead> <tr> <th>Group</th> <th>Number of Male Animals</th> <th>Dose Route</th> <th>Target Dose Level (mg/kg)</th> <th>Target Dose Volume (mL/kg)</th> <th>Samples Collected</th> </tr> </thead> <tbody> <tr> <td>1</td> <td>2</td> <td>Oral</td> <td>3</td> <td>5</td> <td>Blood, Urine, and Feces</td> </tr> </tbody> </table> <p><i>Note: The radioactive dose was approximately 60 µCi/kg.<br/>                 (excerpted from Applicant's report)</i></p> <p><b>Results:</b></p> <ul style="list-style-type: none"> <li>• C<sub>max</sub> and AUC observed in serum were 1820 ng equivalents <sup>14</sup>C-tivozanib/g and 20900 ng equivalents <sup>14</sup>C-tivozanib-hour/g.</li> <li>• The radio-HPLC analysis showed that the oral dose was absorbed and the parent compound (tivozanib) was the predominant circulating component representing an average of approximately 78% of the total radioactivity exposure in serum. Major metabolites M4 (mono-oxidation)/M5 (N-oxide of tivozanib) co-eluting, represented an average of approximately 17% of the total radioactivity exposure in serum. Minor unknown metabolite M44 represented 1% of the total radioactivity exposure in serum.</li> </ul> | Group      | Number of Male Animals    | Dose Route                 | Target Dose Level (mg/kg) | Target Dose Volume (mL/kg) | Samples Collected | 1 | 2 | Oral | 3 | 5 | Blood, Urine, and Feces |
| Group                                      | Number of Male Animals                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | Dose Route | Target Dose Level (mg/kg) | Target Dose Volume (mL/kg) | Samples Collected         |                            |                   |   |   |      |   |   |                         |
| 1                                          | 2                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | Oral       | 3                         | 5                          | Blood, Urine, and Feces   |                            |                   |   |   |      |   |   |                         |

|                                |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
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|                                | <ul style="list-style-type: none"> <li>• In urine, an average of 3.40% of the administered radioactive dose was eliminated within 24 hours postdose. Parent compound was not detected in the urine. None of the metabolites detected in urine represented an average of greater than 0.5% of the administered radioactive dose. Except for M4/M5 co-eluting, all the other metabolites observed in urine could not be identified.</li> <li>• In feces, an average of 27.4% of the administered radioactive dose was eliminated within 24 hours postdose. Parent compound was the predominant radioactive component (average of 20.6%) of the administered radioactive dose. Each of the other metabolites detected [M37/57 co-eluting, M42, and M7 (<i>O</i>-demethylation) represented an average of less than 1% of the administered radioactive dose.</li> </ul> <p><b>Conclusion:</b><br/>         In monkey serum, the parent compound (tivozanib) was the predominant circulating component (78% of the total radioactivity exposure in serum) with the metabolites M4 (mono-oxidation)/M5 (<i>N</i>-oxide of tivozanib) co-eluting. The parent compound was not detected in the urine and none of the metabolites detected in urine represented an average of greater than 0.5% of the administered radioactive dose. In feces, the parent compound was the main component and each of the other metabolites detected [M37/57 co-eluting, M42, and M7 represented an average of less than 1% of the administered radioactive dose. In regard to excretion, the average radioactivity recovery in urine and feces was 3.40 and 27.4% of the administered radioactive dose, respectively.</p> |
| <p><b>Study #:</b> 8201725</p> | <p><b>Title:</b> <i>In Vitro</i> Metabolism of AV-951 in Rat, Monkey, and Human Primary Hepatocytes, and the In Vitro Metabolism of <sup>14</sup>C-AV-951 in Human Primary Hepatocytes</p> <p><b>GLP:</b> No</p> <p><b>Objectives:</b> To determine the rate of metabolism, to profile and identify metabolites of AV-951, <i>in vitro</i>, using rat, monkey, and human primary hepatocytes, and to determine the metabolism of <sup>14</sup>C-AV-951 in human primary hepatocytes.</p> <p><b>Methods:</b></p> <ul style="list-style-type: none"> <li>• AV-951 was incubated with hepatocytes for 0, 30, 60, and 120 minutes at 0.5 and 5 μM concentrations at 37°C.</li> <li>• Samples were analyzed by LC-MS/MS for remaining AV-951 and by qualitative LC-MS/MS to identify the metabolites formed. Additional incubations with human hepatocytes were conducted with <sup>14</sup>C-AV-951 for assessment of human metabolites.</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |

|  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
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|  | <p><b>Results:</b></p> <ul style="list-style-type: none"><li>• AV-951 was metabolized to a small extent by rat and two human donor hepatocytes and to a moderate extent by monkey and one human donor hepatocytes.</li><li>• The hepatic clearance was reported to be, &lt;0.4%, &lt;1.2%, &lt;1% of hepatic blood flow for rat, monkey and human based on &gt; 99% protein binding of AV-951. This represents low (&lt; 25% of blood flow) hepatic clearance in hepatocyte incubations.</li><li>• AV-951 was metabolized mainly by the addition of oxygen, demethylation, glucuronidation, sulfation, or a combination of these pathways.</li><li>• Twenty-two different metabolites (M1-M24) were detected in rat, monkey and human hepatocyte incubations with AV-951, with the exception of M11 which was evident only in human (minor &gt;0.5%) and M10 (Desmethyl, glucuronide) was not evident in the rat. Metabolites M10, M11, M14, M4/M5, M23 and M24 were also observed in incubations of human hepatocyte with <sup>14</sup>C-AV-951. As such these metabolites were considered to be the more prominent human metabolites and of these only M14 (desmethyl glucuronide) was present at &gt;10% of total radioactivity and was designated as a major metabolite. M14 was also a considered major metabolite in the rat and monkey.</li></ul> |
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**Table 5**  
**Summary of identified AV-951 metabolites formed by rat, monkey, and human hepatocytes**

| Metabolite Designation | Retention Time (Minutes) | LC-MS Designation | Transformation                | Species | Observed Levels |
|------------------------|--------------------------|-------------------|-------------------------------|---------|-----------------|
| Positive ESI Mode      |                          |                   |                               |         |                 |
| M8                     | 6.30                     | M633A             | Desmethyl, oxide, glucuronide | H, M    | Trace           |
| M9                     | 10.23                    | M633B             | Desmethyl, oxide, glucuronide | H, M, R | Trace           |
| M10                    | 10.23                    | M617A             | Desmethyl, glucuronide        | H, M    | Minor           |
| M11                    | 10.66                    | M631              | Glucuronide                   | H       | Minor           |
| M12                    | 11.12                    | M633C             | Desmethyl, oxide, glucuronide | H, M    | Trace           |
| M13                    | 11.35                    | M633D             | Desmethyl, oxide, glucuronide | H       | Trace           |
| M14                    | 12.31                    | M617B             | Desmethyl, glucuronide        | H, M, R | Major           |
| M15                    | 13.91                    | M647              | Oxide, glucuronide            | H, M, R | Trace           |
| M16                    | 14.76                    | M551A             | Oxide, sulfate                | H, M, R | Trace           |
| M1                     | 16.43                    | M457A             | Desmethyl, oxide              | H       | Trace           |
| M3                     | 17.36                    | M457C             | Desmethyl, N-oxide            | H, R    | Trace           |
| M17                    | 18.16                    | M551B             | Structure not proposed        | H, M    | Trace           |
| M4                     | 20.37                    | M471A*            | Oxide                         | H, M, R | Minor           |
| M5                     | 20.37                    | M471B*            | N-oxide                       | H, M, R | Minor           |
| M18                    | 21.96                    | M471D             | Oxide                         | H       | Trace           |
| M7                     | 22.50                    | M441              | Desmethyl                     | H, R    | Trace           |
| Parent                 | 26.48                    | AV-951            | NA                            | H, M, R | NA              |
| Negative ESI Mode      |                          |                   |                               |         |                 |
| M19                    | 10.26                    | M537A             | Desmethyl, oxide, sulfate     | H, M    | Trace           |
| M20                    | 11.06                    | M537B             | Desmethyl, oxide, sulfate     | M       | Trace           |
| M21                    | 11.60                    | M537C             | Desmethyl, oxide, sulfate     | H, M    | Trace           |
| M22                    | 14.08                    | M537D             | Desmethyl, oxide, sulfate     | H, M, R | Trace           |
| M23                    | 14.10                    | M521A             | Desmethyl, sulfate            | H, M, R | Minor           |
| M24                    | 15.64                    | M521B             | Desmethyl, sulfate            | H, M, R | Minor           |

Notes: Categorization of metabolites into major, minor, or trace was based on the incubation of 5  $\mu$ M  $^{14}$ C-AV-951 with human hepatocytes for 120 minutes.

A metabolite is categorized as major if it was >10% of the total radioactivity in the sample by HPLC-RAD.

A metabolite is categorized as minor if it was >0.5% of the total radioactivity in the sample by HPLC-RAD.

A metabolite is categorized as trace if it was observed only by mass spectrometry.

\* Co-eluting components.

(excerpted from Applicant's report)

**Conclusion:**

All prominent human metabolites (M1 through M24) were present in both rat and monkey with the exception of M11 (glucuronide), which was unique to human hepatocytes and M10 which was not observed with rat hepatocytes. M14 (desmethyl glucuronide) was present at >10% of total radioactivity and was designated as a major metabolite in human, monkey and rat. The hepatic clearance was low (< 25% of blood flow) in rat, monkey and human. AV-951 appeared to be metabolized mainly by oxidation and demethylation.

**Study #:** DRZZ1027

**Title:** Comparison of the metabolic profile of KRN951 in human, primate, dog and rat liver microsomes and in Supersomes™ over expressing individual human cytochrome P450 isoforms

**GLP:** Yes

**Objectives:**

To investigate species differences in the metabolic profile of KRN951 in human, monkey, dog and rat liver microsomes and to gain information on which human

|  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
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|  | <p>cytochrome P450 (CYP) isoform(s) may be involved in the metabolism of KRN951 to its metabolite(s).</p> <p><b>Methods:</b></p> <ul style="list-style-type: none"><li>• [<sup>14</sup>C] KRN951 (0.500 μM and 5.00 μM) was incubated in the presence of Sprague-Dawley rat, beagle dog, cynomolgus monkey and human liver microsomes for 0, 20, 30, 40, 50 and 60 minutes at a protein concentration of 1.00 mg/mL. Samples were analyzed using HPLC-RAD.</li><li>• To investigate the involvement of CYP isoforms in the metabolism of KRN951 (0.500 μM and 5.00 μM), metabolite formation was assessed in the presence of heterologously expressed human CYP isoforms (Gentest Supersomes).</li></ul> <p><b>Results:</b></p> <ul style="list-style-type: none"><li>• Cytochrome P450 was involved in the metabolism of KRN951.</li><li>• The disappearance of the KRN951 was NADPH-dependent.</li><li>• Based on radio-chromatograms, the metabolic profile of the monkey was shown to be the closest to human, and the dog was shown to be the most different. The dog had the fewest metabolites formed and the lowest rate of disappearance of KRN951.</li><li>• The metabolites formed by rat, dog and monkey were the same as those produced in human liver microsomes with the exception of one metabolite formed by monkey liver microsomes which eluted earlier than any of the four metabolites observed following incubation with human liver microsomes.</li><li>• The major human hepatic CYP isoforms that were involved in the metabolism of KRN951 were CYP3A4 and CYP1A1.</li></ul> |
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|                                | <p>The following tables summarise the formation of various metabolite peaks in each of the species and heterologously expressed CYP isoforms investigated:</p> <table border="1"> <thead> <tr> <th colspan="2"></th> <th colspan="5">Relative Retention Time</th> </tr> <tr> <th>Peak ID in human profile:</th> <th>nd</th> <th>Peak 1</th> <th>Peak 2</th> <th>Peak 3</th> <th>Peak 4</th> </tr> </thead> <tbody> <tr> <td>Species</td> <td>[KRN951] =</td> <td>0.368</td> <td>0.554-0.585</td> <td>0.592-0.604</td> <td>0.661-0.687</td> <td>0.725-0.749</td> </tr> <tr> <td>Rat</td> <td>0.500 µM</td> <td></td> <td>+</td> <td>+</td> <td>+</td> <td>+</td> </tr> <tr> <td>Dog</td> <td>0.500 µM</td> <td></td> <td>+</td> <td></td> <td></td> <td></td> </tr> <tr> <td>Monkey</td> <td>0.500 µM</td> <td></td> <td>++</td> <td></td> <td>++</td> <td></td> </tr> <tr> <td>Human</td> <td>0.500 µM</td> <td></td> <td>+</td> <td>+</td> <td>++</td> <td>+</td> </tr> <tr> <td>Rat</td> <td>5.00 µM</td> <td></td> <td>++</td> <td>++</td> <td>+++</td> <td>++</td> </tr> <tr> <td>Dog</td> <td>5.00 µM</td> <td></td> <td>++</td> <td></td> <td>++</td> <td></td> </tr> <tr> <td>Monkey</td> <td>5.00 µM</td> <td>+++</td> <td>+++</td> <td>++++</td> <td>++++</td> <td>+++</td> </tr> <tr> <td>Human</td> <td>5.00 µM</td> <td></td> <td>+++</td> <td>+++</td> <td>++++</td> <td>+++</td> </tr> </tbody> </table> <p>Where: + represents activities less than 0.500 pmol/mg/min; ++ represents activities between 0.500 and 5.00 pmol/mg/min; +++ represents activities between 5.00 and 15.0 pmol/mg/min and ++++ represents activities greater than 15.0 pmol/mg/min.</p> <table border="1"> <thead> <tr> <th colspan="2"></th> <th colspan="4">Relative Retention Time</th> </tr> <tr> <th>Peak ID in human profile:</th> <th></th> <th>Peak 1</th> <th>Peak 2</th> <th>Peak 3</th> <th>Peak 4</th> </tr> </thead> <tbody> <tr> <td>Species</td> <td>[KRN951] =</td> <td>0.559-0.600</td> <td></td> <td>0.695-0.718</td> <td>0.724</td> </tr> <tr> <td>CYP1A1</td> <td>0.500 µM</td> <td>++</td> <td></td> <td>+</td> <td></td> </tr> <tr> <td>CYP3A4</td> <td>0.500 µM</td> <td>++++</td> <td></td> <td>++</td> <td></td> </tr> <tr> <td>CYP1A1</td> <td>0.500 µM</td> <td></td> <td></td> <td></td> <td></td> </tr> <tr> <td>CYP3A4</td> <td>0.500 µM</td> <td>+++</td> <td></td> <td>++++</td> <td>+++</td> </tr> </tbody> </table> <p>Where: + represents activities less than 0.100 pmol/pmol CYP/min; ++ represents activities between 0.100 and 0.200 pmol/pmol CYP/min; +++ represents activities between 0.200 and 0.500 pmol/pmol CYP/min and ++++ represents activities greater than 0.500 pmol/pmol CYP/min<br/> <i>(excerpted from Applicant's report)</i></p> <p><b>Conclusion:</b><br/>                 CYP3A4 and CYP1A1 are the major human hepatic CYP isoforms involved in the metabolism of KRN951. The metabolic profile of the monkey was shown to be the closest to human and dog was the most different. Metabolites formed by rat, dog and monkey were the same as those produced in human liver microsomes, with the exception of one metabolite in monkey which eluted earlier than any of the four metabolites observed in the other species.</p> |                         |             | Relative Retention Time |             |             |  |  | Peak ID in human profile: | nd | Peak 1 | Peak 2 | Peak 3 | Peak 4 | Species | [KRN951] = | 0.368 | 0.554-0.585 | 0.592-0.604 | 0.661-0.687 | 0.725-0.749 | Rat | 0.500 µM |  | + | + | + | + | Dog | 0.500 µM |  | + |  |  |  | Monkey | 0.500 µM |  | ++ |  | ++ |  | Human | 0.500 µM |  | + | + | ++ | + | Rat | 5.00 µM |  | ++ | ++ | +++ | ++ | Dog | 5.00 µM |  | ++ |  | ++ |  | Monkey | 5.00 µM | +++ | +++ | ++++ | ++++ | +++ | Human | 5.00 µM |  | +++ | +++ | ++++ | +++ |  |  | Relative Retention Time |  |  |  | Peak ID in human profile: |  | Peak 1 | Peak 2 | Peak 3 | Peak 4 | Species | [KRN951] = | 0.559-0.600 |  | 0.695-0.718 | 0.724 | CYP1A1 | 0.500 µM | ++ |  | + |  | CYP3A4 | 0.500 µM | ++++ |  | ++ |  | CYP1A1 | 0.500 µM |  |  |  |  | CYP3A4 | 0.500 µM | +++ |  | ++++ | +++ |
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|                                |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | Relative Retention Time |             |                         |             |             |  |  |                           |    |        |        |        |        |         |            |       |             |             |             |             |     |          |  |   |   |   |   |     |          |  |   |  |  |  |        |          |  |    |  |    |  |       |          |  |   |   |    |   |     |         |  |    |    |     |    |     |         |  |    |  |    |  |        |         |     |     |      |      |     |       |         |  |     |     |      |     |  |  |                         |  |  |  |                           |  |        |        |        |        |         |            |             |  |             |       |        |          |    |  |   |  |        |          |      |  |    |  |        |          |  |  |  |  |        |          |     |  |      |     |
| Peak ID in human profile:      | nd                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | Peak 1                  | Peak 2      | Peak 3                  | Peak 4      |             |  |  |                           |    |        |        |        |        |         |            |       |             |             |             |             |     |          |  |   |   |   |   |     |          |  |   |  |  |  |        |          |  |    |  |    |  |       |          |  |   |   |    |   |     |         |  |    |    |     |    |     |         |  |    |  |    |  |        |         |     |     |      |      |     |       |         |  |     |     |      |     |  |  |                         |  |  |  |                           |  |        |        |        |        |         |            |             |  |             |       |        |          |    |  |   |  |        |          |      |  |    |  |        |          |  |  |  |  |        |          |     |  |      |     |
| Species                        | [KRN951] =                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | 0.368                   | 0.554-0.585 | 0.592-0.604             | 0.661-0.687 | 0.725-0.749 |  |  |                           |    |        |        |        |        |         |            |       |             |             |             |             |     |          |  |   |   |   |   |     |          |  |   |  |  |  |        |          |  |    |  |    |  |       |          |  |   |   |    |   |     |         |  |    |    |     |    |     |         |  |    |  |    |  |        |         |     |     |      |      |     |       |         |  |     |     |      |     |  |  |                         |  |  |  |                           |  |        |        |        |        |         |            |             |  |             |       |        |          |    |  |   |  |        |          |      |  |    |  |        |          |  |  |  |  |        |          |     |  |      |     |
| Rat                            | 0.500 µM                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |                         | +           | +                       | +           | +           |  |  |                           |    |        |        |        |        |         |            |       |             |             |             |             |     |          |  |   |   |   |   |     |          |  |   |  |  |  |        |          |  |    |  |    |  |       |          |  |   |   |    |   |     |         |  |    |    |     |    |     |         |  |    |  |    |  |        |         |     |     |      |      |     |       |         |  |     |     |      |     |  |  |                         |  |  |  |                           |  |        |        |        |        |         |            |             |  |             |       |        |          |    |  |   |  |        |          |      |  |    |  |        |          |  |  |  |  |        |          |     |  |      |     |
| Dog                            | 0.500 µM                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |                         | +           |                         |             |             |  |  |                           |    |        |        |        |        |         |            |       |             |             |             |             |     |          |  |   |   |   |   |     |          |  |   |  |  |  |        |          |  |    |  |    |  |       |          |  |   |   |    |   |     |         |  |    |    |     |    |     |         |  |    |  |    |  |        |         |     |     |      |      |     |       |         |  |     |     |      |     |  |  |                         |  |  |  |                           |  |        |        |        |        |         |            |             |  |             |       |        |          |    |  |   |  |        |          |      |  |    |  |        |          |  |  |  |  |        |          |     |  |      |     |
| Monkey                         | 0.500 µM                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |                         | ++          |                         | ++          |             |  |  |                           |    |        |        |        |        |         |            |       |             |             |             |             |     |          |  |   |   |   |   |     |          |  |   |  |  |  |        |          |  |    |  |    |  |       |          |  |   |   |    |   |     |         |  |    |    |     |    |     |         |  |    |  |    |  |        |         |     |     |      |      |     |       |         |  |     |     |      |     |  |  |                         |  |  |  |                           |  |        |        |        |        |         |            |             |  |             |       |        |          |    |  |   |  |        |          |      |  |    |  |        |          |  |  |  |  |        |          |     |  |      |     |
| Human                          | 0.500 µM                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |                         | +           | +                       | ++          | +           |  |  |                           |    |        |        |        |        |         |            |       |             |             |             |             |     |          |  |   |   |   |   |     |          |  |   |  |  |  |        |          |  |    |  |    |  |       |          |  |   |   |    |   |     |         |  |    |    |     |    |     |         |  |    |  |    |  |        |         |     |     |      |      |     |       |         |  |     |     |      |     |  |  |                         |  |  |  |                           |  |        |        |        |        |         |            |             |  |             |       |        |          |    |  |   |  |        |          |      |  |    |  |        |          |  |  |  |  |        |          |     |  |      |     |
| Rat                            | 5.00 µM                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |                         | ++          | ++                      | +++         | ++          |  |  |                           |    |        |        |        |        |         |            |       |             |             |             |             |     |          |  |   |   |   |   |     |          |  |   |  |  |  |        |          |  |    |  |    |  |       |          |  |   |   |    |   |     |         |  |    |    |     |    |     |         |  |    |  |    |  |        |         |     |     |      |      |     |       |         |  |     |     |      |     |  |  |                         |  |  |  |                           |  |        |        |        |        |         |            |             |  |             |       |        |          |    |  |   |  |        |          |      |  |    |  |        |          |  |  |  |  |        |          |     |  |      |     |
| Dog                            | 5.00 µM                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |                         | ++          |                         | ++          |             |  |  |                           |    |        |        |        |        |         |            |       |             |             |             |             |     |          |  |   |   |   |   |     |          |  |   |  |  |  |        |          |  |    |  |    |  |       |          |  |   |   |    |   |     |         |  |    |    |     |    |     |         |  |    |  |    |  |        |         |     |     |      |      |     |       |         |  |     |     |      |     |  |  |                         |  |  |  |                           |  |        |        |        |        |         |            |             |  |             |       |        |          |    |  |   |  |        |          |      |  |    |  |        |          |  |  |  |  |        |          |     |  |      |     |
| Monkey                         | 5.00 µM                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | +++                     | +++         | ++++                    | ++++        | +++         |  |  |                           |    |        |        |        |        |         |            |       |             |             |             |             |     |          |  |   |   |   |   |     |          |  |   |  |  |  |        |          |  |    |  |    |  |       |          |  |   |   |    |   |     |         |  |    |    |     |    |     |         |  |    |  |    |  |        |         |     |     |      |      |     |       |         |  |     |     |      |     |  |  |                         |  |  |  |                           |  |        |        |        |        |         |            |             |  |             |       |        |          |    |  |   |  |        |          |      |  |    |  |        |          |  |  |  |  |        |          |     |  |      |     |
| Human                          | 5.00 µM                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |                         | +++         | +++                     | ++++        | +++         |  |  |                           |    |        |        |        |        |         |            |       |             |             |             |             |     |          |  |   |   |   |   |     |          |  |   |  |  |  |        |          |  |    |  |    |  |       |          |  |   |   |    |   |     |         |  |    |    |     |    |     |         |  |    |  |    |  |        |         |     |     |      |      |     |       |         |  |     |     |      |     |  |  |                         |  |  |  |                           |  |        |        |        |        |         |            |             |  |             |       |        |          |    |  |   |  |        |          |      |  |    |  |        |          |  |  |  |  |        |          |     |  |      |     |
|                                |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | Relative Retention Time |             |                         |             |             |  |  |                           |    |        |        |        |        |         |            |       |             |             |             |             |     |          |  |   |   |   |   |     |          |  |   |  |  |  |        |          |  |    |  |    |  |       |          |  |   |   |    |   |     |         |  |    |    |     |    |     |         |  |    |  |    |  |        |         |     |     |      |      |     |       |         |  |     |     |      |     |  |  |                         |  |  |  |                           |  |        |        |        |        |         |            |             |  |             |       |        |          |    |  |   |  |        |          |      |  |    |  |        |          |  |  |  |  |        |          |     |  |      |     |
| Peak ID in human profile:      |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | Peak 1                  | Peak 2      | Peak 3                  | Peak 4      |             |  |  |                           |    |        |        |        |        |         |            |       |             |             |             |             |     |          |  |   |   |   |   |     |          |  |   |  |  |  |        |          |  |    |  |    |  |       |          |  |   |   |    |   |     |         |  |    |    |     |    |     |         |  |    |  |    |  |        |         |     |     |      |      |     |       |         |  |     |     |      |     |  |  |                         |  |  |  |                           |  |        |        |        |        |         |            |             |  |             |       |        |          |    |  |   |  |        |          |      |  |    |  |        |          |  |  |  |  |        |          |     |  |      |     |
| Species                        | [KRN951] =                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | 0.559-0.600             |             | 0.695-0.718             | 0.724       |             |  |  |                           |    |        |        |        |        |         |            |       |             |             |             |             |     |          |  |   |   |   |   |     |          |  |   |  |  |  |        |          |  |    |  |    |  |       |          |  |   |   |    |   |     |         |  |    |    |     |    |     |         |  |    |  |    |  |        |         |     |     |      |      |     |       |         |  |     |     |      |     |  |  |                         |  |  |  |                           |  |        |        |        |        |         |            |             |  |             |       |        |          |    |  |   |  |        |          |      |  |    |  |        |          |  |  |  |  |        |          |     |  |      |     |
| CYP1A1                         | 0.500 µM                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | ++                      |             | +                       |             |             |  |  |                           |    |        |        |        |        |         |            |       |             |             |             |             |     |          |  |   |   |   |   |     |          |  |   |  |  |  |        |          |  |    |  |    |  |       |          |  |   |   |    |   |     |         |  |    |    |     |    |     |         |  |    |  |    |  |        |         |     |     |      |      |     |       |         |  |     |     |      |     |  |  |                         |  |  |  |                           |  |        |        |        |        |         |            |             |  |             |       |        |          |    |  |   |  |        |          |      |  |    |  |        |          |  |  |  |  |        |          |     |  |      |     |
| CYP3A4                         | 0.500 µM                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | ++++                    |             | ++                      |             |             |  |  |                           |    |        |        |        |        |         |            |       |             |             |             |             |     |          |  |   |   |   |   |     |          |  |   |  |  |  |        |          |  |    |  |    |  |       |          |  |   |   |    |   |     |         |  |    |    |     |    |     |         |  |    |  |    |  |        |         |     |     |      |      |     |       |         |  |     |     |      |     |  |  |                         |  |  |  |                           |  |        |        |        |        |         |            |             |  |             |       |        |          |    |  |   |  |        |          |      |  |    |  |        |          |  |  |  |  |        |          |     |  |      |     |
| CYP1A1                         | 0.500 µM                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |                         |             |                         |             |             |  |  |                           |    |        |        |        |        |         |            |       |             |             |             |             |     |          |  |   |   |   |   |     |          |  |   |  |  |  |        |          |  |    |  |    |  |       |          |  |   |   |    |   |     |         |  |    |    |     |    |     |         |  |    |  |    |  |        |         |     |     |      |      |     |       |         |  |     |     |      |     |  |  |                         |  |  |  |                           |  |        |        |        |        |         |            |             |  |             |       |        |          |    |  |   |  |        |          |      |  |    |  |        |          |  |  |  |  |        |          |     |  |      |     |
| CYP3A4                         | 0.500 µM                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | +++                     |             | ++++                    | +++         |             |  |  |                           |    |        |        |        |        |         |            |       |             |             |             |             |     |          |  |   |   |   |   |     |          |  |   |  |  |  |        |          |  |    |  |    |  |       |          |  |   |   |    |   |     |         |  |    |    |     |    |     |         |  |    |  |    |  |        |         |     |     |      |      |     |       |         |  |     |     |      |     |  |  |                         |  |  |  |                           |  |        |        |        |        |         |            |             |  |             |       |        |          |    |  |   |  |        |          |      |  |    |  |        |          |  |  |  |  |        |          |     |  |      |     |
| <p><b>Study #:8133-100</b></p> | <p><b>Title:</b> <i>In Vitro</i> Metabolism of AV-951 in Human Hepatic Microsomes<br/> <b>GLP:</b> No<br/> <b>Objectives:</b> To determine the rate of metabolism and to profile and identify metabolites of AV-951, <i>in vitro</i>, using human hepatic microsomes.</p> <p><b>Methods:</b> AV-951 was incubated with microsomes for 0, 15, 30, and 60 minutes at a concentration of 0.5 and 5 µM. The samples were analyzed by LC-MS/MS for remaining AV-951 and qualitative LC-MS/MS to identify the metabolites formed.</p> <p><b>Results:</b></p> <ul style="list-style-type: none"> <li>AV-951 was metabolized to a small extent by human hepatic microsomes, mainly through oxidation and demethylation.</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |                         |             |                         |             |             |  |  |                           |    |        |        |        |        |         |            |       |             |             |             |             |     |          |  |   |   |   |   |     |          |  |   |  |  |  |        |          |  |    |  |    |  |       |          |  |   |   |    |   |     |         |  |    |    |     |    |     |         |  |    |  |    |  |        |         |     |     |      |      |     |       |         |  |     |     |      |     |  |  |                         |  |  |  |                           |  |        |        |        |        |         |            |             |  |             |       |        |          |    |  |   |  |        |          |      |  |    |  |        |          |  |  |  |  |        |          |     |  |      |     |

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|                                            | <ul style="list-style-type: none"> <li>• Seven metabolites were reported (M1 to M7) to be formed in the process.</li> <li>• The hepatic clearance was determined to be low (&lt;25% of blood flow).</li> </ul> <p><b>Conclusion:</b><br/>         AV-951 was metabolized to a small extent by human hepatic microsomes, mainly through oxidation and demethylation. The hepatic clearance was low. Seven metabolites were reported (M1 to M7) to be formed in the process.</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
| <p><b>Study #:</b><br/> <b>8231061</b></p> | <p><b>Title:</b> Evaluation of AV-951 on Cytochrome P450 Induction using Primary Cultures of Human Hepatocytes<br/> <b>GLP:</b> No</p> <p><b>Objectives:</b> To measure the extent of induction of specific P450 marker enzymes (for CYP1A, 2B6, 2C9, 2C19, and 3A) and relative mRNA concentrations following exposure of human hepatocytes to AV-951, and to compare the effects of AV-951 with those of prototypical inducers.</p> <p><b>Methods:</b><br/>         Primary hepatocyte cultures were exposed to AV-951 at 0.1, 0.5, or 5 µM, prototypical CYP inducers, or representative solvent controls for 72 hours. CYP isoenzyme activities were evaluated by determining the rate of production of relevant metabolites utilizing LC-MS/MS detection.</p> <p><b>Results/Conclusion:</b><br/>         Exposure to 0.1, 0.5, and 5 µM AV-951 did not cause substantial increases (&lt;40%) in CYP1A, CYP2B6, CYP2C9, CYP2C19 or CYP3A enzyme activities. The data suggested that drug to drug interaction resulting from induction of CYPs enzyme activities by AV-951 was unlikely.</p> |
| <p><b>Study #:</b><br/> <b>8231062</b></p> | <p><b>Title:</b> Determination of the Apparent Permeability of <sup>14</sup>C-AV-951 through Caco-2 Monolayers and Evaluation as a P-gp Substrate and Inhibitor<br/> <b>GLP:</b> No</p> <p><b>Objectives:</b> To determine the apparent permeability and P-glycoprotein (P-gp) interaction of <sup>14</sup>C-AV-951 using human colon carcinoma cell line (Caco-2 cells).</p> <p><b>Methods:</b> The Caco-2 permeability assay was run at 0.1, 0.5 and 5 µM [<sup>14</sup>C]-tivozanib hydrochloride. The Trans Epithelial Electric Resistance values of the monolayers prior to the experiment were measured and the apparent permeability of paracellular, transcellular, and P-gp efflux marker compounds at 1 µM was determined. Each compound was incubated for 1 hour in the same manner as described for the test article.</p>                                                                                                                                                                                                                                                           |

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|                                                | <p><b>Results/Conclusion:</b><br/>                 It was reported that <sup>14</sup>C-AV-951 has low permeability (1.30 to 4.41 x 10<sup>-6</sup> cm/s) in Caco-2 cell monolayers. <sup>14</sup>C-AV-951 did not appear to be a substrate of P-gp. At higher concentrations, <sup>14</sup>C-AV-951 inhibited P-gp mediated transport of 3H-digoxin.</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
| <p><b>Study #:</b><br/> <b>8242516</b></p>     | <p><b>Title:</b> Identification of Human UGT Isoenzymes Involved in the Metabolism of <sup>14</sup>C-Tivozanib and Associated Inhibitory Interactions<br/> <b>GLP:</b> No<br/> <b>Objectives:</b><br/>                 To determine the involvement of specific uridine diphosphate-glucuronosyltransferase (UGT) isoenzymes in the metabolism of <sup>14</sup>C-tivozanib using cDNA expressed human UGTs, and to determine the general inhibitory potential of tivozanib towards microsomal UGT activity.</p> <p><b>Methods:</b></p> <ul style="list-style-type: none"> <li>• The identification of UGT isoenzymes involved in the metabolism of <sup>14</sup>C-tivozanib were determined by incubation of the test article with cDNA expressed human UGTs. The rate of disappearance of <sup>14</sup>C-tivozanib or metabolite formation was determined.</li> <li>• The inhibitory effects of tivozanib on human hepatic UGT activity were determined by measuring the effect of the test article on the metabolism of UGT marker substrates, 4-methylumbelliferone and para-nitrophenol.</li> </ul> <p><b>Results/Conclusion:</b></p> <ul style="list-style-type: none"> <li>• Substantial levels of <sup>14</sup>C-tivozanib desmethyl glucuronide metabolites were formed by UGT isoenzymes.</li> <li>• Metabolite M14, a desmethyl glucuronide metabolite, was the major metabolite formed by six UGT enzymes. Other observed glucuronide metabolites were M10 and M25. Since the major metabolite (M14) was formed by six different UGT isoenzymes, inhibition of any one of these enzymes was not likely to cause substantial drug-drug interactions.</li> <li>• Tivozanib inhibited glucuronidation of UGT substrates 4-MU and p-NP to a small extent. Therefore, tivozanib is not a potent inhibitor of UGT activities.</li> </ul> |
| <p><b>Study #:</b><br/> <b>AV951-08274</b></p> | <p><b>Title:</b> <i>In vitro</i> Biotransformation of Tivozanib (AV-951)<br/> <b>GLP:</b> No<br/> <b>Objectives:</b> To determine the formation of metabolic products of tivozanib (AV-951) by human liver microsomes <i>in vitro</i>, and the extent to which the biotransformation is inhibited by ketoconazole, temsirolimus, and everolimus.</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |

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|                                             | <p><b>Methods:</b></p> <ul style="list-style-type: none"> <li>• A fixed concentration of triazolam (250 µM - CYP3A4 substrate) was added to varying concentrations of tivozanib hydrochloride (0 to 500 µM). Ketoconazole (0.1 µM) and troleandomycin (TAO) (5 µM) were used as index inhibitors.</li> <li>• Incubations were performed without preincubation of inhibitors with the substrate, followed by incubation with preincubation of inhibitors with microsomes prior to addition of the substrate. HPLC analysis was used to evaluate the metabolites.</li> </ul> <p><b>Results/Conclusion:</b></p> <ul style="list-style-type: none"> <li>• Tivozanib was biotransformed to at least four metabolic products by human liver microsomes.</li> <li>• Tivozanib inhibited biotransformation, with IC<sub>50</sub> values of 1.1- 2.0 µM for Ketoconazole, and &gt; 50 µM for temsirolimus, and everolimus.</li> <li>• Tivozanib was shown to be a weak inhibitor of CYP3A.</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                             |
| <p><b>Study #:</b><br/> <b>DRZZ1040</b></p> | <p><b>Title:</b> Whole Body Phosphor Imaging in Male and Female Rats Following a Single Oral Administration of [<sup>14</sup>C] KRN951</p> <p><b>GLP:</b> Yes</p> <p><b>Objectives:</b> To provide quantitative data on the tissue distribution of compound related radioactivity in male and female albino and male pigmented rats following a single oral administration of [<sup>14</sup>C] KRN951 at a target dose level of 1 mg/kg.</p> <p><b>Methods:</b></p> <ul style="list-style-type: none"> <li>• Twelve male albino, 4 female albino and 6 male pigmented rats were used.</li> <li>• Rats were dosed orally once with 1 mg/kg of [<sup>14</sup>C] KRN951 (10 mL/kg).</li> <li>• Tissue concentrations of radioactivity were quantified from each of the rats at different time points.</li> <li>• An image representing the distribution of radioactivity across whole body sections at each time point was taken.</li> <li>• A whole blood sample collected from each rat immediately prior to sacrifice was analyzed for radioactivity by liquid scintillation counting.</li> </ul> <p><b>Results/Conclusion:</b></p> <ul style="list-style-type: none"> <li>• The highest concentrations of radioactivity were observed in the contents of the gastrointestinal tract.</li> <li>• Distribution of radioactivity was similar between sexes and strains of rats.</li> </ul> |

|                                             |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
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|                                             | <ul style="list-style-type: none"> <li>• The extent of tissue penetrance was low, with tissue/blood ratios of less than 1 in the majority of tissues.</li> <li>• Maximal tissue concentrations were observed at 4 hours post-dose.</li> <li>• Highest radioactivity tissue concentrations were measured in the preputial gland, Harderian gland, white fat and liver.</li> <li>• Lowest radiation levels were in the spinal cord and brain.</li> <li>• In 24 hours post-dose the majority of radiation was eliminated from tissues, and by 72 hours post-dose the radiation levels were below the limit of quantification.</li> <li>• No sex differences were reported in the majority of tissues, with concentrations in both the ovary and uterus being very similar to blood levels, and those in testes being significantly less than that in blood.</li> <li>• Melanin binding was apparent and levels decreased over 120 hours post-dose.</li> </ul>                                                                                                                                                                                                                                                                           |
| <p><b>Study #:</b><br/> <b>DRZZ1039</b></p> | <p><b>Title:</b> Determination of the <i>In Vitro</i> Binding of [<sup>14</sup>C] KRN951 to Plasma Proteins in Rat, Monkey and Human</p> <p><b>GLP:</b> Yes</p> <p><b>Objectives:</b> To provide information on <i>the in vitro</i> binding of [<sup>14</sup>C] KRN951 to the plasma proteins of male and female rat, monkey and human.</p> <p><b>Methods:</b></p> <ul style="list-style-type: none"> <li>• Concentration of [<sup>14</sup>C] KRN951: 50, 500 and 5000 ng/mL</li> <li>• The binding of tivozanib hydrochloride to plasma proteins in male and female Sprague-Dawley rat, cynomolgus monkey and human plasma was determined by equilibrium dialysis on pooled male and female rat and monkey plasma samples and on individual male and female human plasma samples. Total protein and albumin was determined.</li> </ul> <p><b>Results/Conclusion:</b></p> <ul style="list-style-type: none"> <li>• Plasma protein binding for the rat and human were very similar (99.3% and 99.7%).</li> <li>• Monkey plasma protein binding results were lower (97.6%).</li> <li>• The free fraction was lower in the human and rat samples compared to monkey samples.</li> <li>• No gender differences were reported.</li> </ul> |
| <p><b>Study #:</b><br/> <b>8236152</b></p>  | <p><b>Title:</b> The <i>In Vitro</i> Protein Binding of <sup>14</sup>C-Tivozanib to Human Plasma and Serum, Albumin and Human <math>\alpha</math>1-Acid Glycoprotein, Protein Binding Interactions, and Human Blood to Plasma Partitioning</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |

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|                                            | <p><b>GLP:</b> Yes</p> <p><b>Objectives:</b><br/>                 To determine, <i>in vitro</i>: 1) the extent of binding of <sup>14</sup>C-tivozanib to plasma and serum proteins from human; 2) the potential for serum protein binding interactions between <sup>14</sup>C-tivozanib and warfarin in human serum; 3) the partitioning of <sup>14</sup>C-tivozanib between blood and plasma; and 4) the extent of binding of <sup>14</sup>C-tivozanib to isolated human plasma proteins, <i>i.e.</i>, human serum albumin (HSA) and α1-acid glycoprotein (AAG).</p> <p><b>Methods:</b></p> <ul style="list-style-type: none"> <li>• The protein binding of the radiolabeled test article was determined at concentrations of 0.1, 0.3, 1, 3 and 5 μM in human plasma and serum and in HSA and AAG solutions using the equilibrium dialysis method.</li> <li>• The effect of tivozanib at concentrations of 0, 0.1, 0.3, 1, 3 and 5 μM on the protein binding of a single concentration of <sup>3</sup>H-warfarin (2μg/mL) in human serum was evaluated.</li> <li>• The effect warfarin at 0, 1, 3 and 6 μM on a single concentration of <sup>14</sup>C-tivozanib in human serum on protein binding was evaluated.</li> <li>• The blood-to-plasma partitioning of <sup>14</sup>C-tivozanib was determined at concentrations of 0.1, 0.3, 1, 3 and 5 μM in human blood. Initially, the time to reach equilibrium was determined by incubating male human blood with a single concentration of <sup>14</sup>C-tivozanib for up to 60 minutes.</li> </ul> <p><b>Results/Conclusion:</b></p> <ul style="list-style-type: none"> <li>• HSA was considered the major tivozanib binding component of human plasma and serum, based on <sup>14</sup>C-tivozanib binding to human plasma and serum proteins and to HSA and AAG with percent bound &gt;99% and 50%, respectively.</li> <li>• Tivozanib at concentrations of 0 to 5 μM and 0 to 6 μM did not alter the serum protein binding of <sup>3</sup>H-warfarin at 2 μg/mL and 0.5 μg/mL. The data suggested that protein binding interactions between tivozanib and warfarin were unlikely.</li> <li>• <sup>14</sup>C-tivozanib partitions mainly into the plasma/serum compartment based on the mean blood-to-plasma ratio ranged from 0.53 to 0.62 across human donors.</li> </ul> |
| <p><b>Study #:</b><br/> <b>PKP0227</b></p> | <p><b>Title:</b> KRN951 Serum Kinetics Experiment in Nude Rats</p> <p><b>GLP:</b> No</p> <p><b>Objectives:</b> To determine the pharmacokinetic profile of KN951 administered in a single oral dose to Nude rats.</p> <p><b>Methods:</b></p> <ul style="list-style-type: none"> <li>• Female nude rats</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |

- Age of 8 weeks
- Single dose of KRN951 (Lot # M-001)

**Study design:**

| Group | Dosage Concentration | Dosage Amount | Number of Rats |
|-------|----------------------|---------------|----------------|
| B     | 0.004 mg/mL          | 0.04 mg/kg    | 4              |
| C     | 0.02 mg/mL           | 0.2 mg/kg     | 4              |
| D     | 0.1 mg/mL            | 1 mg/kg       | 4              |
| E     | 0.5 mg/mL            | 5 mg/kg       | 4              |

*(excerpted from Applicant's report)*

- Blood was taken at 0.5, 1, 2, 4, 8, 24, 48 and 72 hours post-dose for pharmacokinetic analysis.
- Serum samples were analyzed using HPLC-MS/MS.
- Endpoints:  $C_{max}$ , AUC,  $T_{1/2}$ ,  $T_{max}$

**Results/Conclusion:**

- Systemic exposure ( $C_{max}$  and AUC) increased proportionally with dose (0.04 to 5 mg/kg).
- The  $T_{max}$  values were 2.63 – 4.25 hours.
- The  $t_{1/2}$  of 7.8 – 9.3 hours.

**Table 2** Pharmacokinetic parameters after single oral administration of KRN951 to female nude rats

| Dose       | animal No. | AUC (µg hr/mL) | Cl/F (mL/hr/kg) | Vd/F (mL/kg) | T1/2 (hr) | Cmax (ng/mL) | Tmax (hr) |
|------------|------------|----------------|-----------------|--------------|-----------|--------------|-----------|
| 0.04 mg/kg | B-1        | 0.275          | 145             | 1689         | 8.05      | 19.0         | 4.00      |
|            | B-2        | 0.446          | 89.7            | 1062         | 8.21      | 22.5         | 4.00      |
|            | B-3        | 0.328          | 122             | 1587         | 9.04      | 22.0         | 2.50      |
|            | B-4        | 0.307          | 130             | 2196         | 11.7      | 22.7         | 4.00      |
|            | mean       | 0.339          | 122             | 1634         | 9.25      | 21.6         | 3.63      |
|            | S.D.       | 0.075          | 23              | 465          | 1.69      | 1.7          | 0.75      |
| 0.2 mg/kg  | C-1        | 1.38           | 145             | 1673         | 8.02      | 100          | 2.50      |
|            | C-2        | 1.81           | 111             | 1213         | 7.60      | 119          | 4.00      |
|            | C-3        | 1.90           | 105             | 1084         | 7.13      | 121          | 2.00      |
|            | C-4        | 1.48           | 135             | 1626         | 8.35      | 91.0         | 2.00      |
|            | mean       | 1.64           | 124             | 1399         | 7.78      | 108          | 2.63      |
|            | S.D.       | 0.25           | 19              | 295          | 0.53      | 15           | 0.95      |
| 1 mg/kg    | D-1        | 6.44           | 155             | 1607         | 7.18      | 464          | 1.00      |
|            | D-2        | 8.33           | 120             | 1144         | 6.61      | 542          | 4.00      |
|            | D-3        | 8.05           | 124             | 1940         | 10.8      | 520          | 4.00      |
|            | D-4        | 7.72           | 130             | 1482         | 7.93      | 409          | 8.00      |
|            | mean       | 7.64           | 132             | 1543         | 8.13      | 484          | 4.25      |
|            | S.D.       | 0.83           | 16              | 329          | 1.86      | 60           | 2.87      |
| 5 mg/kg    | E-1        | 49.1           | 102             | 1243         | 8.47      | 2514         | 8.00      |
|            | E-2        | 40.7           | 123             | 1391         | 7.84      | 2426         | 2.00      |
|            | E-3        | 45.2           | 111             | 1135         | 7.11      | 3480         | 2.00      |
|            | E-4        | 43.0           | 116             | 1403         | 8.35      | 2872         | 2.00      |
|            | mean       | 44.5           | 113             | 1293         | 7.94      | 2823         | 3.50      |
|            | S.D.       | 3.6            | 9               | 128          | 0.62      | 479          | 3.00      |

(excerpted from Applicant's report)

Modeling using the average serum concentration data from the 0.2 mg/kg dose group indicates that after multiple administrations, a dose of 0.2 mg/kg/day would result in an average serum concentration at steady state of 69.5 ng/mL.

**Table 3** Simulated Serum concentrations after multiple oral administration of KRN951 at a dose of 0.2 mg/kg/day to female nude rats

| Dose (mg/kg/day) | τ (hr) | Vd/F (mL/kg) | ka (hr <sup>-1</sup> ) | ke (hr <sup>-1</sup> ) | C <sup>ss</sup> max (ng/mL) | C <sup>ss</sup> min (ng/mL) | C <sup>ss</sup> avg (ng/mL) |
|------------------|--------|--------------|------------------------|------------------------|-----------------------------|-----------------------------|-----------------------------|
| 0.2              | 24     | 1297         | 0.615                  | 0.0924                 | 124                         | 22.2                        | 69.5                        |

(excerpted from Applicant's report)

**Study #:**  
**AV951-**  
**08028**

**Title:** Pharmacokinetics in Female Ncr Nu/Nu Mice After a Single Oral Dose of 5 or 20 mg/kg Tivozanib Hydrochloride  
**GLP:** No

| <p><b>Objectives:</b> To determine the pharmacokinetic profile of KN951 administered in a single oral dose to Nude mice.</p> <p><b>Methods:</b></p> <ul style="list-style-type: none"><li>• Seven-week old female nude mice</li><li>• Single dose of KRN951</li><li>• KRN951 Lot # CDM-003</li><li>• Oral gavage</li><li>• Doses of 5 or 20 mg/kg</li><li>• Blood was taken at 0, 0.25, 0.5, 1, 2, 4, 8, 16, 24, and 48 hours postdose for pharmacokinetic analysis.</li><li>• Serum samples were analyzed using HPLC-MS/MS.</li><li>• Endpoints: <math>C_{max}</math>, AUC, <math>T_{1/2}</math>, <math>T_{max}</math></li></ul> <p><b>Results/conclusion:</b></p> <ul style="list-style-type: none"><li>• <math>C_{max}</math> at the 5 and 20 mg/kg dose levels was 1361 and 7708 ng/mL, respectively.</li><li>• AUC was 11513 and 68233 hr·ng/mL for the 5 and 20 mg/kg doses, respectively.</li><li>• Both the <math>C_{max}</math> and AUC showed dose-dependent increases.</li><li>• The <math>t_{1/2}</math> for 5 and 20 mg/kg was not dose dependent, being 6.11 and 4.58 hours, respectively.</li></ul> <p><b>Table 3: Mean Pharmacokinetic Parameters following a Single Oral Administration to Female Nude Mice (Study AV951-08028)</b></p> <table border="1"><thead><tr><th>Dose (mg/kg)</th><th><math>C_{max}</math><sup>a</sup> (ng/mL)</th><th><math>T_{max}</math> (hr)</th><th>AUC<sub>0-∞</sub> (hr·ng/mL)<sup>a</sup></th><th><math>t_{1/2}</math> (hr)</th></tr></thead><tbody><tr><td>5</td><td>1361</td><td>2</td><td>11513</td><td>6.11</td></tr><tr><td>20</td><td>7708</td><td>2</td><td>68233</td><td>4.58</td></tr></tbody></table> <p><sup>a</sup>Units for AUC and <math>C_{max}</math> were converted from micrograms/L. to nanograms/mL.<br/>(excerpted from Applicant's report)</p> | Dose (mg/kg)                   | $C_{max}$ <sup>a</sup> (ng/mL) | $T_{max}$ (hr)                             | AUC <sub>0-∞</sub> (hr·ng/mL) <sup>a</sup> | $t_{1/2}$ (hr) | 5 | 1361 | 2 | 11513 | 6.11 | 20 | 7708 | 2 | 68233 | 4.58 |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------|--------------------------------|--------------------------------------------|--------------------------------------------|----------------|---|------|---|-------|------|----|------|---|-------|------|
| Dose (mg/kg)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | $C_{max}$ <sup>a</sup> (ng/mL) | $T_{max}$ (hr)                 | AUC <sub>0-∞</sub> (hr·ng/mL) <sup>a</sup> | $t_{1/2}$ (hr)                             |                |   |      |   |       |      |    |      |   |       |      |
| 5                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | 1361                           | 2                              | 11513                                      | 6.11                                       |                |   |      |   |       |      |    |      |   |       |      |
| 20                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | 7708                           | 2                              | 68233                                      | 4.58                                       |                |   |      |   |       |      |    |      |   |       |      |

## 6 General Toxicology

### Overall Summary:

Single-oral and intravenous (IV) dose toxicity studies in CD-1 mice and Sprague-Dawley (SD) rats were conducted followed by oral repeat-dose studies in SD rats (up to 26 weeks) and cynomolgus monkeys (up to 39 weeks).

*IV single-dose:* the maximum tolerated dose in mice and rats following a single IV administration was established to be greater than the highest dose tested of 30 mg/kg, which also is the maximum feasible dose.

Given that the oral route is the proposed clinical route, the studies used to assess the safety of the compound in support of the current NDA application were performed using the oral route as follows.

*Oral single-dose studies:* In mice, a single-oral dose of tivozanib at 524 mg/kg (1700-fold of the recommended human dose) was considered to be the maximum tolerated dose. A dose of 524 mg/kg, resulted in a decrease in body weight gain, reduced lymphocyte count, total white blood cell count and increases in ALT, AST, ALP.

In rats, a single-oral dose of tivozanib at 276 mg/kg (1790-fold of the recommended human dose) was considered to be the maximum tolerated dose. A dose of 276 mg/kg, resulted in a decrease in body weight, increases in RBC parameters, ALT, AST and urobilinogen.

*Oral repeat-dose studies in rats:* In the repeat-dose toxicology studies, rats were orally dosed with tivozanib for 13 weeks (0.01, 0.03, 0.1, 0.3, or 1.0 mg/kg/day) and 26 weeks (0.005, 0.02 or 0.08 mg/kg/day). In the 13-week rat study, doses  $\geq 0.1$  mg/kg/day resulted in mortalities and severe clinical observations (clinical signs typically associated with morbidity, malocclusion, missing teeth and white teeth) with effects more pronounced at 1 mg/kg/day, resulting in cessation of dosing at 1 mg/kg/day after 4 weeks of dosing. Body weights and food consumption were decreased throughout the treatment period at doses  $\geq 0.03$  mg/kg/day. These decreases were accompanied by test article-related changes in clinical pathology parameters. The hematology parameters reported at doses  $\geq 0.03$  mg/kg/day included decreases in red blood cell parameters and at doses  $\geq 0.1$  mg/kg/day increases in white blood cell parameters (lymphocytes, monocytes and neutrophils). Clinical chemistry changes included increase in iron metabolism at doses  $\geq 0.03$  mg/kg/day; decrease in protein parameters and increase in liver parameters at doses  $\geq 0.1$  mg/kg/day; increases in LDH/creatinine, triglycerides and renal parameters at 1 mg/kg/day. Test article-related urinalysis changes were reported at doses  $\geq 0.1$  mg/kg/day (increased protein); at doses  $\geq 0.3$  mg/kg/day (increased urobilinogen and bilirubin) and at 1 mg/kg/day (increased hyaline casts). Test article-related macroscopic findings and organ weights were reported in multiple organs in both sexes at doses  $\geq 0.3$  mg/kg/day and doses  $\geq 0.01$  mg/kg/day, respectively. Macroscopic findings associated with test article-related microscopic findings were reported at doses  $\geq 0.1$  mg/kg/day in both sexes. In general, the incidence and/or severity of the findings were dose-dependent. At doses  $\geq 0.1$  mg/kg/day the target organs with significant toxicity observed were adrenal glands, kidney, bone femur, liver and bile duct, brain, pituitary, incisors, pancreas and duodenum. Less pronounced (lower incidence and/or severity) microscopic findings were reported in the heart, reproductive organs, bone marrow, adrenal medulla and stomach. The NOAEL was considered to be 0.03 mg/kg/day (HED = 0.29g/day, or 0.2X the recommended human dose) based on adverse microscopic findings. Toxicities at doses  $\geq 0.3$ mg/kg/day were significant and many were not recoverable. Partial recovery of most effects was reported at doses  $\geq 0.1$  mg/kg/day, although renal effects were not recoverable at these doses. In the 26-week rat study, findings of white teeth (doses  $\geq 0.005$  mg/kg/day), decreases in body weights, hematology findings (increases in leukocytes, hemoglobin, hematocrit and erythrocytes) and clinical chemistry findings (decreases in total protein, albumin and globulins

in both sexes) were reported at 0.08 mg/kg/day. The above observed effects were not considered to be adverse, and no additional test article-related findings were reported by the end of the treatment or the recovery periods. The NOAEL was established to be the highest dose tested, 0.08 mg/kg/day (HED = 0.78g/day; or 0.5-fold the recommended human dose).

*Oral repeat-dose studies in monkeys:* In the repeat-dose toxicology studies, monkeys were orally dosed with tivozanib for 13 weeks (0.01, 0.03, 0.1, 0.3 or 1 mg/kg/day) and 39 weeks (0.005, 0.01, 0.02, 0.03 or 0.08 mg/kg/day). In the 13-week monkey study, a dose of 1.0 mg/kg was considered severely toxic, and therefore, dosing was ceased after approximately 4 weeks of dosing. Doses  $\geq$  0.3 mg/kg/day resulted in clinical signs and decrease in body weights. Test article-related hematological changes were evident at 1 mg/kg/day (increases in RBC parameters, fibrin and M/E ratio; decreases in WBC, RETIC, NEUT, MCV and PT). Test article-related clinical and urine chemistry changes were evident at 1 mg/kg/day (increases in CK, SELA- $\alpha$  &  $\beta$ , iron, phospholipids; decreases in ALP, SDH, total bile acid, amylase, UIBC, U LDH, U creatinine). The clinical chemistry changes reported at doses  $\geq$  0.1 mg/kg/day (increases in SELA- $\alpha$ , CK, and phospholipids) were considered test article-related, but changes were of lesser magnitude. Some of clinical pathology changes were attributed to the reported body weight changes. At doses  $\geq$  0.3 mg/kg/day, significant decreases in absolute and relative thymus weights was reported. Macroscopic findings were only evident at 1 mg/kg/day. The predominant test article-related microscopic findings were evident at doses  $\geq$  0.3 mg/kg/day and included bone (femur and tibia), gastric system (stomach, duodenum and pancreas), reproductive system (ovary and corpora lutea), adrenal cortex, lymphoid depletion of lymphoid organs (thymus, lymph nodes and spleen) and brain. At doses  $\geq$  0.1 mg/kg/day, brain and adrenal cortex were affected. The majority of the findings were recoverable after a 2-week recovery period at 1 mg/kg. All of the findings at 0.1 and 0.3 mg/kg/day were recoverable during the 5-week recovery period. The NOAEL was established to be 0.1 mg/kg/day (HED = 1.95 g/day; 1.3-fold of the recommended human dose).

In a 39-week monkey study, the highest dose tested (0.1 mg/kg/day) was well tolerated. No test article-related clinical observations were reported. There were no effects on body weight, clinical pathology, echocardiographic, ECG, macro and microscopic findings reported at all dose levels. The NOAEL was established to be 0.1 mg/kg/day (HED=1.95 g/day; 1.3-fold of the maximum recommended human dose).

Overall, both the 26-week rat and 39-week monkey toxicology studies were insufficient, as the highest dose(s) assessed produced no/minimal toxicity and dose-response relationships could not be evaluated. Given the low safety margin noted for this study in regard to the clinical dose, it is uncertain why the Applicant did not explore a more robust range of doses in these studies. Given the lack of substantial toxicity in these studies, the Applicant proposed to use the data from the 13-week rat and monkey studies to inform the package insert regarding toxicities in nonclinical studies.

## **6.1 Single-Dose Toxicity**

**Key findings:**

Single oral and intravenous dose toxicity studies were performed in CD-1 mice and Sprague-Dawley rats to establish the maximum tolerated dose for tivozanib.

- In mice, a single oral dose of 524 mg/kg (1700-fold the recommended human dose) was considered to be the maximum tolerated dose. At doses  $\geq$  750 mg/kg, mortality and clinical observations were reported. At doses  $\geq$  524 mg/kg, a decrease in body weight gain, reduced lymphocyte count, total white blood cell count and increases in ALT, AST, ALP were reported.
- In rats, a single oral dose of 276 mg/kg (1790-fold the recommended human dose) was considered to be the maximum tolerated dose. Higher doses resulted in mortalities (369 mg/kg and 2000 mg/kg) and clinical observations. A decrease in body weight was observed in all dose groups. At 276 mg/kg, increases in RBC parameters, ALT, AST and urobilinogen were reported.
- An IV dose  $>$  30 mg/kg (the maximal feasible dose) was established to be the maximum tolerated dose in mice and rats (97- and 195-fold the recommended human dose for mice and rats, respectively).

**Reviewer comment:** *The Toxicokinetic data was not reviewed and discussed in this section for the following reason. The bioanalyses and toxicokinetic data supporting the single-dose toxicology studies (RZZ1008, RZZ 1009, RZZ 1010 and RZZ 1011) were compromised due to data integrity issues and non-compliance with the GLP regulations. As such, the data were not considered reliable, and the Applicant amended the final reports and excluded the data.*

|                                   |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
|-----------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Study #:</b><br><b>RZZ1008</b> | <p><b>Title:</b> Acute Intravenous Toxicity Study in the Rat with KRN951 Including Toxicokinetic Sampling</p> <p><b>GLP:</b> Yes, with the exception of bioanalytical and toxicokinetic (TK) analysis.</p> <p><b>Objectives:</b> to evaluate the maximum tolerated dose and to assess the acute toxicity of KRN951, an angiogenesis inhibitor in the Sprague Dawley rats following a single dose by intravenous (IV) injection.</p> <p><b>Methods:</b> All rats (5/sex/group) received a single dose of the test article at 30 mg/kg (the highest soluble dose of KRN951 in vehicle) or the vehicle (40% Dimethylacetamide) by the IV route. Rats were observed up to 14 days post-dose. Endpoints: body weights, clinical pathology, urine, necropsy and TK.</p> <p><b>Results:</b></p> <ul style="list-style-type: none"><li>• Clinical observations were evident only during the first 15 minutes post-dose, which included subdued behavior, agitation and abnormal gait.</li><li>• No effects were reported on body weights. On Day 4, red blood cells, hemoglobin, hematocrit and mean hemoglobin concentration levels were increased, while platelet counts, neutrophils and reticulocytes were reduced in males and females. By Day 15 the changes in red cell</li></ul> |
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|                                            |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
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|                                            | <p>parameters and platelets were not evident. Clinical chemistry parameters were increased on Day 4 (ALT, AST, Fe, cholesterol and phospholipids), while unsaturated iron binding capacity was decreased. By Day 15 the changes were not evident. A decrease in osmolality of the urine was evident on Day 1, but not on Day 14.</p> <p><b>Conclusion:</b><br/>         A dose &gt; 30 mg/kg was considered to be the maximum tolerated dose in rats treated IV with a single dose of KRN951.</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
| <p><b>Study #:</b><br/> <b>RZZ1010</b></p> | <p><b>Title:</b> Acute Intravenous Toxicity Study in the Mouse with KRN951 Including Toxicokinetic Sampling<br/> <b>GLP:</b> Yes, with the exception of bioanalytical and TK analysis<br/> <b>Objectives:</b> to evaluate the maximum tolerated dose and to assess the acute toxicity of KRN951 in the CD-1 mouse following a single dose by IV injection.</p> <p><b>Methods:</b> Mice received a single dose of KRN951 (15/sex/group) at 30 mg/kg (the highest soluble dose of KRN951 in vehicle) or the vehicle (40% Dimethylacetamide) by the IV route. Mice were observed for up to 14 Days post-dose.<br/>         Endpoints: body weights, clinical pathology, necropsy and TK.</p> <p><b>Results:</b></p> <ul style="list-style-type: none"> <li>• No clinical observations or effects on body weights were reported.</li> <li>• Transient changes in hematology (decrease in reticulocytes) were reported on Day 4. No effects on clinical chemistry parameters were reported.</li> </ul> <p><b>Conclusion:</b><br/>         A dose of &gt; 30 mg/kg was considered to be the maximum tolerated dose in CD-1 mice treated IV with a single dose of KRN951.</p> |
| <p><b>Study #:</b><br/> <b>RZZ1011</b></p> | <p><b>Title:</b> Acute Oral Toxicity Study in the Mouse with KRN951 Including Toxicokinetic (TK) Sampling<br/> <b>GLP:</b> Yes, with the exception of bioanalytical and TK analysis<br/> <b>Objectives:</b> to evaluate the maximum tolerated dose and to assess the acute toxicity of KRN951 in the CD-1 mouse following a single dose by oral gavage.</p> <p><b>Methods:</b> Mice received a single oral dose of the test article.<br/> <i>In phase 1:</i> Doses of 369, 750 and 1000 mg/kg were administered to 2mice/sex/group. Mice were observed for up to 7 days post-dose.<br/> <i>In phase 2:</i> 15 mice/sex/group were dosed with 0.5% methylcellulose or 524 mg/kg KRN951. Mice were observed for up to 15 days post-dose. Blood was</p>                                                                                                                                                                                                                                                                                                                                                                                                                   |

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|                                            | <p>collected for clinical pathology and urine for urinalysis. Necropsy was performed at the end of the observation period.<br/> <i>In phase 3:</i> 14 mice/sex were dosed orally with 524 mg/kg and bled for TK analysis.</p> <p><b>Results:</b></p> <ul style="list-style-type: none"> <li>• One male mouse at 750 mg/kg and one at 1000 mg/kg were terminated due to severe signs of toxicity at approximately 7 and 4 hours post-dose on Day 1, respectively.</li> <li>• At doses <math>\geq</math> 750 mg/kg clinical observations were reported that included tremors, subdued behavior, piloerection, cold, dilated pupils, abnormal gait and/or pale ears. No clinical observations were reported at doses <math>\leq</math> 524 mg/kg.</li> <li>• At doses <math>\geq</math> 524 mg/kg a decrease of up to 13% in body weight gain was reported.</li> <li>• At 524 mg/kg lymphocyte count and total white blood cell count were reduced on Day 2.</li> <li>• ALT, AST and ALP were increased at 524 mg/kg.</li> </ul> <p><b>Conclusion:</b><br/>                 A dose of 524 mg/kg was considered to be the maximum tolerated dose in CD-1 mice treated orally with a single dose of KRN951.</p>                                                                                                     |
| <p><b>Study #:</b><br/> <b>RZZ1009</b></p> | <p><b>Title:</b> Acute Oral Toxicity Study in the Rat with KRN951 Including Toxicokinetic Sampling<br/> <b>GLP:</b> Yes, with the exception of bioanalytical and TK analysis<br/> <b>Objectives:</b> To evaluate the maximum tolerated dose and to assess the acute toxicity of KRN951 in Sprague Dawley rat following a single dose by oral gavage.</p> <p><b>Methods:</b> Rats received a single oral dose of the test article.<br/> <i>In phase 1:</i> Doses of 369, 1000 or 2000 mg/kg were given orally to 2 rats/sex/group. Rats were observed for up to 7 Days post-dose.<br/> <i>In phase 2:</i> 5 rats/sex/group were dosed with 0.5% methylcellulose or 276 mg/kg KRN951. Rats were observed for up to 14 Days post-dose. Blood was collected for clinical pathology and urine for urinalysis. Necropsy was performed at the end of the observation period.<br/> <i>In phase 3:</i> 14 rats/sex were dosed orally with 400 mg/kg and bled for TK analysis.</p> <p><b>Results:</b></p> <ul style="list-style-type: none"> <li>• One male at 369 mg/kg was found dead on Day 8 and one female at 2000 mg/kg was terminated on Day 6.</li> <li>• Clinical observations were reported at 369 mg/kg (hunched posture and piloerection), 1000 mg/kg (piloerection and distended abdomen) and at</li> </ul> |

|  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
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|  | <p>2000 mg/kg (distended abdomen, irregular breathing, subdued behavior, piloerection, abnormal gait, emaciation, weight loss, hunched posture, tremors (male only), restless behavior, pale ears and lack of coordination).</p> <ul style="list-style-type: none"> <li>• A decrease in body weight was reported at all dose groups (up to 10% at doses <math>\leq</math> 1000 mg/kg and up to 24% at 2000 mg/kg).</li> <li>• At 276 mg/kg hematology parameters (red blood cells, hemoglobin and hematocrit) were increased on Day 2 and decreased on Day 15. Lymphocyte count (Lymph) and total white blood cell count (WBC) were reduced while neutrophils were increased at Day 2.</li> <li>• At 276 mg/kg ALT and AST were increased on Day 2.</li> <li>• At 276 mg/kg urobilinogen was increased on Day 3.</li> </ul> <p><b>Conclusion:</b><br/>         A dose of 276 mg/kg was considered to be the maximum tolerated dose in rats treated orally with a single dose of KRN951.</p> |
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## 6.2 Repeat-Dose Toxicity

**Reviewer comment:** *The Toxicokinetic data for study 6691-158 was not reviewed and discussed in this section for the following reason: the bioanalyses and toxicokinetic data was compromised due to data integrity issues and non-compliance with the GLP regulations. As such, the data was not considered reliable, and the Applicant amended the final report and excluded the data.*

| Study title: 13-Week Oral Gavage Toxicity and Toxicokinetic Study with a 5-Week Recovery Period with KRN951 in Rats |                                                                                    |
|---------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------|
| Study no.:                                                                                                          | 6691-158                                                                           |
| Sponsor:                                                                                                            | Kyowa Hakko Kirin Co., Ltd.,<br>(formerly Kirin Brewery Co., Ltd),<br>Tokyo, Japan |
| Conducting laboratory and location:                                                                                 | (b) (4)                                                                            |
| Date of study initiation:                                                                                           | 07 July, 2003                                                                      |
| GLP compliance/QA statement:                                                                                        | Yes, with the exception of bioanalytical and TK analyses                           |
| Drug, lot #, and % purity:                                                                                          | KRN951, CDM-001 and 98.8%                                                          |

### Key Findings:

- The NOAEL was considered to be 0.03 mg/kg/day (HED = 0.29g/day, or 0.2X the recommended human dose) based on adverse microscopic findings.
- Test article-related **mortalities** were reported at doses  $\geq$  0.1 mg/kg/day in male and female rats.

- Test article-related **clinical observations** were reported at doses  $\geq 0.1$  mg/kg/day in male and female rats with effects more pronounced at 1 mg/kg/day, resulting in cessation of dosing at 1 mg/kg/day after 4 weeks of dosing.
  - Clinical observations included clinical signs typically associated with morbidity, malocclusion, missing teeth and white teeth. Treatment-related white teeth and malocclusion persisted throughout the recovery period.
- Test article-related decrease in mean **body weight** was reported at  $\geq 0.03$ , mg/kg/day (-13% to -38%) throughout the treatment period, and at  $\geq 0.3$  mg/kg/day (up to -25%) at the end of the recovery period.
- Test article-related decrease in **food consumption** was reported (both sexes) at  $\geq 0.03$  mg/kg/day during the treatment period. Findings persisted at doses  $\geq 0.3$  mg/kg/day throughout the recovery period.
- Test article-related changes in **hematology** parameters were reported at doses  $\geq 0.03$  mg/kg/day and included decreases in red blood cell parameters. At doses  $\geq 0.1$  mg/kg/day increases in white blood cell parameters (lymphocytes, monocytes and neutrophils) were reported. Most changes persisted at the end of recovery.
- **Clinical chemistry** changes included increase in iron metabolism at doses  $\geq 0.03$  mg/kg/day; decrease in protein parameters and increase in liver parameters at doses  $\geq 0.1$  mg/kg/day; increases in LDH/creatinine, triglycerides and renal parameters at 1 mg/kg/day. At the end of the recovery period, no test article-related findings were reported at doses  $\leq 0.1$  mg/kg/day, however, effects at doses  $\geq 0.3$  mg/kg/day persisted.
- Test article-related **urine changes** were reported at doses  $\geq 0.1$  mg/kg/day (increased protein); at doses  $\geq 0.3$  mg/kg/day (increased urobilinogen and bilirubin) and at 1 mg/kg/day (increased hyaline casts). At the end of the recovery period, findings persisted at doses  $\geq 0.1$  mg/kg/day.
- Test article-related **macroscopic findings** were reported in both sexes at doses  $\geq 0.3$  mg/kg/day (in adrenal gland; duodenum, pancreas, testis, epididymis and seminal vesicle; missing teeth and mandibular lymph nodes). At the end of the recovery period, macroscopic findings were only reported at 1 mg/kg/day and they included pale adrenal cortex and kidney.
- Test article-related increases in a number of relative **organ weights** were reported at doses  $\geq 0.01$  mg/kg/day. At the end of the recovery period, effects on relative organ weights persisted at  $\geq 0.3$  mg/kg/day.
- Test article-related **microscopic findings** were reported at doses  $\geq 0.1$  mg/kg/day in both sexes. In general, the incidence and/or severity of the findings were dose-dependent.
  - At doses  $\geq 0.1$  mg/kg/day the target organs with significant toxicity observed were adrenal glands (congestion/hemorrhage, degeneration and necrosis), kidney (glomerulopathy and chronic nephropathy), bone femur (hypertrophy of the physis and loss of the primary spongiosa), liver and bile duct (inflammation and biliary hypertrophy/hyperplasia), brain (vacuolated cells in choroid plexus and choroid vessel necrosis), pituitary (hypertrophic and degenerate chromophobe cells), incisors (degeneration of odontoblasts, ameloblasts and

- dentin dysplasia at doses  $\geq 0.3$  mg/kg/day), pancreas (atrophy) and duodenum (transmural and mucosal hypertrophy).
- Less pronounced (lower incidence and/or severity) microscopic findings were reported in the heart (focal necrosis and myofiber degeneration), reproductive organs (atrophy of the ovaries and uterus), bone marrow (hypocellularity), adrenal medulla (necrosis) and stomach (congestion, hyperplasia/metaplasia of fundic epithelium).
  - By the end of the recovery period, most microscopic findings at doses  $\geq 0.3$  mg/kg/day showed partial recovery, except for the microscopic findings in the kidney, which were not recoverable.

Tissues showing partial recovery included brain, adrenal cortex, bone marrow, bone, heart, pancreas, ovary, uterus and teeth at 1 mg/kg/day;; adrenal cortex, and duodenum at 0.3 mg/kg/day; brain, heart, liver; kidney, pancreas, uterus, bone and bone marrow at 0.1 and 0.3 mg/kg/day.

**Methods:**

NDA/BLA Multi-disciplinary Review and Evaluation {NDA 212904}  
 {FOTIVDA, tivozanib}

**Doses/ Number/Sex/Group:** Male and female rats were assigned to treatment Groups 1-6 with 30, 10, 10, 15, 15 and 15 animals/sex/group, respectively.  
 Group 1 received vehicle control (0.5% MC); and Groups 2 through 6 received 0.01, 0.03, 0.1, 0.3, or 1.0 mg/kg/day, respectively.

**Route/Frequency of dosing:** Oral gavage/Daily  
**Dose volume:** 10 mL/kg  
**Formulation/Vehicle:** Vehicle, 0.5% methylcellulose  
**Sex/Species/Strain:** Male and female Crl:CD®(SD) IGS BR rats  
**Age/Weight:** 8 weeks /  
 238 to 285 g for the males, and  
 172 to 214 g for the females.

**Toxicokinetic evaluation:** 5 rats per sex per group were assigned to evaluating the Toxicokinetic (TK) at each dose level (Groups 7 through 11, respectively).

**Endpoints evaluated:** Mortality, clinical observations, ophthalmic examinations, body weight, weight gain, food consumption, organ weights, macroscopic findings, clinical pathology and microscopic findings.  
 Clinical pathology (hematology, Chemistry, coagulation, and urine): were collected based on the following schedule:

| <b>Week</b>             | <b>Dose</b>                            |
|-------------------------|----------------------------------------|
| 4 (terminal Sacrifice)  | Control and 1 mg/kg/day                |
| 7 (interim recovery)    | Control and 1 mg/kg/day                |
| 12 (terminal sacrifice) | 0.3 mg/kg/day                          |
| 14 (terminal sacrifice) | Control, 0.01, 0.03, and 0.1 mg/kg/day |
| 19 (terminal recovery)  | Control, 0.1 and 0.3 mg/kg/day         |

**Termination and necropsy:**

- Interim (week 4): 1 mg/kg/day and control dose group.
- Recovery (week 7): 1 mg/kg/day and control dose group.
- Terminal: 0.3 mg/kg/day on week 12; control, 0.01, 0.03, and 0.1 mg/kg/day on week 14.
- Recovery (week 19): control, 0.1 and 0.3 mg/kg/day.

Deviation from study protocol: None of the deviations affected the integrity or interpretability of the study.

*Results:*

**Mortalities**

Test article-related mortalities were reported at doses  $\geq 0.1$  mg/kg/day:

- Three male and three female rats at 1 mg/kg/day were found dead or moribund sacrificed during weeks 3-4.
- At 0.3 mg/kg/day, three male and three female rats were found dead or moribund sacrificed during weeks 7- 12 of the study.
- One female was found dead at 0.1 mg/kg/day during week 5.
- All found dead or moribund sacrificed rats at doses  $\geq 0.3$  mg/kg/day, were associated with microscopic findings of adrenal necrosis/degeneration. The animal found dead at 0.1 mg/kg/day, had urinary tract inflammation and adrenal necrosis.

**Mortalities:**

| Dose (mg/kg/day)  | Sex    | Day of moribund sacrifice | Day of found dead | Gavage error     | Histopathological associated findings       |
|-------------------|--------|---------------------------|-------------------|------------------|---------------------------------------------|
| 0 (Main)          | Female | –                         | Day 23 (week 4)   | –                | cause of death undetermined                 |
| 0.01 (Main)       | Male   | –                         | –                 | Day 69 (week 10) | perforation of the esophagus (gavage error) |
| 0.1 (Main)        | Female | –                         | Day 34 (week 5)   | –                | urinary tract inflammation                  |
| <b>0.3 (Main)</b> | Male   | –                         | Day 68 (week 10)  | –                | Adrenal necrosis/degeneration               |
| <b>0.3 (Main)</b> | Male   | Day 43 (week 7)           | –                 | –                | Adrenal necrosis/degeneration               |
| <b>0.3 (Main)</b> | Male   | –                         | Day 78 (week 12)  | –                | Adrenal necrosis/degeneration               |
| <b>0.3 (Main)</b> | Female | Day 46 (week 7)           | –                 | –                | Adrenal necrosis/degeneration               |
| <b>0.3 (Main)</b> | Female | Day 79 (week 12)          | –                 | –                | Adrenal necrosis/degeneration               |
| <b>0.3 (TK)</b>   | Female | –                         | Day 45 (week 7)   | –                | –                                           |
| <b>1.0 (Main)</b> | Male   | Day 24 (week 4)           | –                 | –                | Adrenal necrosis/degeneration               |
| <b>1.0 (Main)</b> | Male   | Day 25 (week 4)           | –                 | –                | Adrenal necrosis/degeneration               |

|                   |        |                    |                    |   |                                  |
|-------------------|--------|--------------------|--------------------|---|----------------------------------|
| <b>1.0 (Main)</b> | Male   | Day 16<br>(week 3) | –                  | – | Adrenal<br>necrosis/degeneration |
| <b>1.0 (Main)</b> | Female | Day 20<br>(week 4) | –                  | – | Adrenal<br>necrosis/degeneration |
| <b>1.0 (Main)</b> | Female | –                  | Day 23<br>(week 4) | – | Adrenal<br>necrosis/degeneration |
| <b>1.0 (TK)</b>   | Female | –                  | Day 16<br>(week 3) | – | –                                |

TK= Toxicokinetic;

**Bolded = treatment-related**

- = no t applicable

### Clinical Observations

Test article-related clinical observations were reported at doses  $\geq 0.3$  mg/kg/day in male and female rats and included hunched, thin, hypoactive, rough hair coat, yellow hair coat, cold to touch, pale, malocclusion, missing teeth and white teeth. Additionally, test article-related effects were evident in males at 0.1 mg/kg/day which included, rough hair coat and malocclusion.

White teeth and malocclusion at doses  $\geq 0.3$  mg/kg/day persisted throughout the recovery period.

### Clinical observations:

| Observation       | Number of rats affected |   |                   |   |                   |   |                  |   |                  |    |                |   |
|-------------------|-------------------------|---|-------------------|---|-------------------|---|------------------|---|------------------|----|----------------|---|
|                   | 0                       |   | 0.01<br>mg/kg/day |   | 0.03<br>mg/kg/day |   | 0.1<br>mg/kg/day |   | 0.3<br>mg/kg/day |    | 1<br>Mg/kg/day |   |
|                   | M                       | F | M                 | F | M                 | F | M                | F | M                | F  | M              | F |
| Hunched           | 0                       | 0 | 1                 | 0 | 0                 | 0 | 0                | 0 | 11               | 7  | 3              | 1 |
| Missing teeth     | 1                       | 0 | 0                 | 0 | 0                 | 0 | 0                | 0 | 11               | 11 | 0              | 0 |
| Thin              | 0                       | 0 | 0                 | 0 | 0                 | 0 | 1                | 0 | 13               | 15 | 0              | 6 |
| Hypoactive        | 0                       | 0 | 1                 | 0 | 0                 | 0 | 0                | 0 | 3                | 2  | 0              | 1 |
| Rough hair coat   | 0                       | 1 | 1                 | 1 | 0                 | 0 | 3                | 0 | 14               | 9  | 5              | 6 |
| Yellow hair coat  | 0                       | 0 | 0                 | 0 | 0                 | 0 | 0                | 0 | 3                | 4  | 0              | 1 |
| Cold to touch     | 0                       | 0 | 0                 | 0 | 0                 | 0 | 0                | 0 | 2                | 1  | 1              | 0 |
| Pale              | 0                       | 0 | 0                 | 0 | 0                 | 0 | 0                | 0 | 3                | 1  | 1              | 1 |
| Malocclusion      | 1                       |   | 0                 | 0 | 1                 | 0 | 4                | 0 | 14               | 6  | 0              | 0 |
| White teeth-upper | 0                       | 0 | 0                 | 0 | 0                 | 1 | 0                | 0 | 12               | 13 | 3              | 2 |
| White teeth-lower | 1                       | 8 | 0                 | 0 | 1                 | 3 | 1                | 2 | 14               | 15 | 4              | 9 |

M=male; F=female

**Bolded = treatment-related**

### Body Weight

At 1 mg/kg/day test article-related decreases in mean body weights were reported in males (m) and females (f) during the first 4 weeks of treatment (by up to 33% in males and 26% in females), and at the end of the interim recovery period, body weight decreases persisted (up 38% in males and 19% in females). Throughout the period, (weeks 1 to 13), mean body weights in males and females were lower than control by up to 15% and 9% at 0.1 mg/kg/day, respectively, and by up to 41% and 32% at 0.3 mg/kg/day. The decreases in mean body weights persisted throughout the recovery period at 0.3 mg/kg/day (by up to 25% in males and 21% in females). Decreases in mean body weights were also reported in females at 0.03 mg/kg/day (up to 13% in females) during weeks 8 to 13. No effect on mean body weight was reported at the end of the recovery period at 0.03 mg/kg/day. In general, the effects were more pronounced in males at all dose groups.

**Mean body weight (% Change):**

| Days   | % Change in Mean Body Weight |    |                   |    |                   |     |                  |    |                  |     |                |     |
|--------|------------------------------|----|-------------------|----|-------------------|-----|------------------|----|------------------|-----|----------------|-----|
|        | 0                            |    | 0.01<br>mg/kg/day |    | 0.03<br>mg/kg/day |     | 0.1<br>mg/kg/day |    | 0.3<br>mg/kg/day |     | 1<br>Mg/kg/day |     |
|        | M                            | F  | M                 | F  | M                 | F   | M                | F  | M                | F   | M              | F   |
| 1-25   | NS                           | NS | NS                | NS | NS                | NS  | NS               | NS | NS               | NS  | -33            | -26 |
| 25-43  | NS                           | NS | NS                | NS | NS                | NS  | -8               | -9 | -33              | -20 | -38            | -19 |
| 43-60  | NS                           | NS | NS                | NS | NS                | NS  | -8               | -9 | -28              | -26 |                |     |
| 60-92  | NS                           | NS | NS                | NS | NS                | -13 | -15              | -9 | -41              | -32 |                |     |
| 1-92   | NS                           | NS | NS                | NS | NS                | -13 | -15              | -9 | -41              | -32 |                |     |
| 92-127 | NS                           | NS |                   |    |                   |     | NS               | NS | -25              | -21 |                |     |

Only statistically significant findings were listed in this table

M=male; F=female; -=decrease

Day 24 for males and 23 for females - end of treatment for 1 mg/kg/day and start of the recovery period until day 44.

Day 92 end of treatment; recovery period ends on day 127 for doses ≤ 0.3 mg/kg/day.

Shaded area: Data was not collected per protocol; NS=not significant

**Body Weight Gain**

Male rats gained up to 10%, 15% and 97% less weight at 0.1, 0.3 and 1 mg/kg/day relative to controls during the first 25 days of treatment, respectively. For the entire treatment period (Days 1-92) male rats gained up to 10%, 7%, 17% and 63% at 0.01, 0.03, 0.1 and 0.3 mg/kg/day, less body weight than the control animals, respectively. Female rats gained up to 19%, 19%, 18% and 99% less weight at 0.03, 0.1, 0.3 and 1 mg/kg/day relative to controls during the first 25 days of treatment, respectively. For the entire treatment period (Days 1-92) female rats gained up to 15%, 30%, 20% and 45% at 0.01, 0.03, 0.1 and 0.3 mg/kg/day, less body weight than the control animals, respectively. No test article-related effects were reported at the end of the recovery period.

**Body weight gain (% change):**

| Days | % Body Weight Gain |   |                   |   |                   |   |                  |   |                  |   |                |   |
|------|--------------------|---|-------------------|---|-------------------|---|------------------|---|------------------|---|----------------|---|
|      | 0                  |   | 0.01<br>mg/kg/day |   | 0.03<br>mg/kg/day |   | 0.1<br>mg/kg/day |   | 0.3<br>mg/kg/day |   | 1<br>mg/kg/day |   |
|      | M                  | F | M                 | F | M                 | F | M                | F | M                | F | M              | F |

|        |    |    |     |    |    |     |     |     |     |     |     |     |
|--------|----|----|-----|----|----|-----|-----|-----|-----|-----|-----|-----|
| 1-25   | NS | NS | NS  | NS | NS | -19 | -10 | -19 | -15 | -18 | -97 | -99 |
| 1-92   | NS | NS | -15 | NS | -7 | -30 | -17 | -20 | -63 | -45 |     |     |
| 92-127 | NS | NS |     |    |    |     | NS  | NS  | NS  | NS  |     |     |

M=male; F=female; minus sign =decrease; Shaded area and NS=not significant.

### Food Consumption

Test article-related decreases in food consumption were reported at 1 mg/kg/day in male and female rats during the first 25 days of treatment (up to 55% in males and 56% in females). Decreases in food consumption were also reported during the entire treatment period (Days 1-92) in males and females at 0.3 mg/kg/day (46% in males and 50% in females), at 0.1 mg/kg/day (up to 11% in males and 14% in females) and at 0.03 mg/kg/day in females (up to 13% in females). Food consumption values continued to be lower than the control group values at the end of the recovery period at doses  $\geq$  0.3 mg/kg/day (up to 1% in males and 15% in females).

### Food consumption (% change):

| Days                  | 0.01 mg/kg/day |    | 0.03 mg/kg/day |     | 0.1 mg/kg/day |     | 0.3 mg/kg/day |     | 1 <sup>1</sup> mg/kg/day |                  |
|-----------------------|----------------|----|----------------|-----|---------------|-----|---------------|-----|--------------------------|------------------|
|                       | M              | F  | M              | F   | M             | F   | M             | F   | M                        | F                |
| 1-25                  | NS             | NS | NS             | NS  | -10           | -7  | -8            | -10 | -55                      | -56              |
| 25-43                 | NS             | NS | NS             | -7  | -10           | -14 | -45           | -47 | -55 <sup>1</sup>         | -29 <sup>1</sup> |
| 43-92                 | NS             | NS | NS             | -13 | -11           | -11 | -46           | -50 |                          |                  |
| 1-92                  | NS             | NS | NS             | NS  | -11           | -14 | -46           | -50 |                          |                  |
| R 92-127 <sup>2</sup> |                |    |                |     | NS            | NS  | -18           | -15 |                          |                  |

Only statistically significant and biologically relevant findings were listed in this table

<sup>1</sup> Day 23/24 marked the end of treatment at 1 mg/kg/day, (recovery period for this group was days 24-44).

<sup>2</sup> Day 92 was end of treatment, and recovery period ended on day 127 for all remaining doses  $\leq$  0.3 mg/kg/day.

Shaded area- no data/ recovery group available

NS= Not statistically significant

Any rat showing evidence of teeth abnormalities and all 0.3 and 1.0 mg/kg/day rats were given meal-form diet to facilitate feed intake.

R=recovery

**Ophthalmology:** No test article-related ophthalmic findings were reported.

### Hematology

At 1 mg/kg/day, test article-related significant changes were reported in:

- Males, red blood cells parameters, platelet, neutrophils (NEUT), monocytes, APTT, and myeloid/erythroid (M/E) ratio during week 4. At the end of the recovery period (week 7) the following parameters were still evident: red blood cells (RBC), reticulocytes (RETIC), Absolute reticulocytes (AB RETIC), MCV and Monocytes.
- Females, red blood cells parameters, AB RETIC, platelet, and M/E ratio during week 4. At the end of the recovery period (week 7) the following parameters were still evident: RBC, mean corpuscular hemoglobin (MCH) and fibrinogen (Fibrin).

At 0.3 mg/kg/day test article-related significant changes were reported in:

- Males, red blood cells parameters RETIC, AB RETIC, platelet, white blood cell (WBC), NEUT, lympho and Mono during week 7. Monocyte values were still higher than controls at the end of the recovery period (week 19).
- Females, hemoglobin (HGB), hematocrit (HCT), WBC, NEUT, lymphocytes and monocytes during week 7. Monocyte values were still higher than controls at the end of the recovery period (week 19).

At 0.1 mg/kg/day test article-related significant changes were reported in:

- Males, red blood cells parameters during week 7/14.
- Females, red blood cells parameters during week 7/14.

Recovery: No findings in both sexes were reported at the end of the recovery period (week 19).

At 0.03 mg/kg/day test article-related significant effects were reported in:

- Females, red blood cells parameters, RETIC and AB RETIC during week 7/14.
- Recovery: No findings in both sexes were reported at the end of the recovery period (week 19).

At 0.01 mg/kg/day the only test article-related change was reported in female HGB (week 14).

***Hematology: Percent change from control***

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| Dose (mg/kg /day) /Sex | M    | F        | M    | F                    | M       | F                    | M                      | F       | M         | F                    |
|------------------------|------|----------|------|----------------------|---------|----------------------|------------------------|---------|-----------|----------------------|
|                        | 0.01 | 0.01     | 0.03 | 0.03                 | 0.1     | 0.1                  | 0.3                    | 0.3     | 1         | 1                    |
| RBC                    | NS   | NS       | NS   | 6 (wk7);<br>8 (wk14) | 6 (wk7) | 6 (wk7)              | 8 (wk7)                | NS      | -20 (wk7) | -9 (wk4); -26 (wk7)  |
| RETIC                  | NS   | NS       | NS   | -35 (wk14)           | NS      | NS                   | -57 (wk7)              | NS      | 59 (wk7)  | NS                   |
| AB RETIC               | NS   | NS       | NS   | -27 (wk14)           | NS      | NS                   | -54 (wk7)              | NS      | 87 (wk7)  | -16 (wk4)            |
| HGB                    | NS   | 4 (wk14) | NS   | 5 (wk7);<br>6 (wk14) | 6 (wk7) | 6 (wk7);<br>7 (wk14) | 11 (wk7);<br>6 (wk 14) | 6 (wk7) | NS        | NS                   |
| HCT                    | NS   | NS       | NS   | 6 (wk14)             | 5 (wk7) | 6 (wk7);<br>6 (wk14) | 9 (wk7)                | 6 (wk7) | NS        | NS                   |
| MCH                    | NS   | NS       | NS   | NS                   | NS      | NS                   | NS                     | NS      | NS        | 6 (wk4);<br>13 (wk7) |

|           |    |    |    |    |                  |    |                                |                  |                        |           |
|-----------|----|----|----|----|------------------|----|--------------------------------|------------------|------------------------|-----------|
| MCV FL    | NS | NS | NS | NS | NS               | NS | NS                             | NS               | 5 (wk4);<br>14 (wk7)   | 6 (wk4)   |
| MCV PG    | NS | NS | NS | NS | 3 (wk14)         | NS | NS                             | NS               | 5 (wk4);<br>12 (wk7)   | 16 (wk7)  |
| Platelet  | NS | NS | NS | NS | NS               | NS | 32 (wk7)                       |                  | 48 (wk4)               | -30 (wk4) |
| WBC       | NS | NS | NS | NS | NS               | NS | 55 (wk7)                       | 93 (wk7)         | NS                     | NS        |
| NEUT      | NS | NS | NS | NS | <b>25 (wk14)</b> | NS | <b>84 (wk7)<br/>173 (wk19)</b> | <b>100 (wk7)</b> | <b>77 (wk4)</b>        | NS        |
| Lympho    | NS | NS | NS | NS | NS               | NS | 43 (wk7)                       | 95 (wk7)         | NS                     | NS        |
| Mono      | NS | NS | NS | NS | NS               | NS | 100 (wk7)                      | 50 (wk7)         | 100 (wk4);<br>50 (wk7) | NS        |
| M/E ratio | NS | NS | NS | NS | NS               | NS | NS                             | NS               | -67 (wk4)              | -62 (wk4) |

Only statistically significant findings were listed in this table.

Bolded: predominate changes.

NS= Not statistically significant; (wk)=week

### Clinical Chemistry

Predominant treatment-related clinical chemistry changes:

- Protein parameters (total protein, albumin, albumin/globulin ration): parameters were decreased at doses  $\geq 0.1$  mg/kg/day. Total protein and albumin were evident at a lesser magnitude at the end of the recovery period.
- Liver parameters: ALT was increased at doses  $\geq 0.1$  mg/kg/day, total bilirubin, Gamma-Glutamyltransferase (U GGT), LDH and triglycerides were increased at 1 mg/kg/day. No findings were reported at the end of the recovery period.
- LDH/creatinine was increased at 1 mg/kg/day and effect on LDH/creatinine at a lesser magnitude was evident at the end of the recovery period.
- Iron metabolism parameters: U Iron binding capacity and percent saturation of transferrin (%SAT) were increased at doses  $\geq 0.03$  mg/kg/day. Serum iron was increased at 0.3 mg/kg/day.
- Renal parameters: Urea nitrogen was increased at doses  $\geq 0.3$  mg/kg/day and urea creatinine at 1 mg/kg/day. Effect on Urea nitrogen at a lesser magnitude was evident at the end of the recovery period.

#### Clinical chemistry (% change):

| Dose (mg/kg/day) /Sex             | M    | F    | M    | F    | M        | F    | M         | F   | M         | F         |
|-----------------------------------|------|------|------|------|----------|------|-----------|-----|-----------|-----------|
|                                   | 0.01 | 0.01 | 0.03 | 0.03 | 0.1      | 0.1  | 0.3       | 0.3 | 1         | 1         |
| ALT                               | NS   | NS   | NS   | NS   | 20 (wk7) | NS   | 183 (wk7) | NS  | 183       | 187       |
| % saturation of transferrin (SAT) | NS   | NS   | NS   | 19   | 38       | 38   | 181       | 81  | 106       | NS        |
| Urea nitrogen                     | NS   | NS   | NS   | 21   | 27       | 21   | NS        | 40  | 143 (73)  | 69 (153)  |
| Urea Creatinine                   | NS   | NS   | NS   | NS   | NS       | NS   | NS        | NS  | 20        | 43        |
| ALK P                             | NS   | NS   | NS   | NS   | NS       | NS   | NS        | NS  | -51 (116) | NS        |
| Total protein                     | -4   | -9   | -6   | NS   | -11      | -14  | -5        | -16 | -22 (-11) | -26 (-12) |
| Albumin                           | NS   | NS   | -7   | NS   | -11      | -15  | -18 (-14) | -33 | -28       | -33 (-22) |
| Albumin/globulin                  | NS   | NS   | NS   | NS   | NS       | NS   | -31 (-21) | NS  | -19       | -35       |
| SELA-ALB                          | NS   | NS   | NS   | NS   | -14      | -16  | -21       | -31 | -39       | -39 (-27) |
| Total Bilirubin                   | NS   | NS   | NS   | NS   | NS       | NS   | NS        | NS  | 100       | NS        |
| Inorganic phosphorus              | NS   | NS   | NS   | NS   | NS       | NS   | NS        | NS  | -18 (16)  | -16       |
| Triglycerides                     | NS   | NS   | NS   | NS   | NS       | NS   | NS        | NS  | 251 (71)  | 84 (384)  |
| Glucose                           | NS   | NS   | -21  | NS   | -9       | NS   | NS        | NS  | 21 (22)   | NS        |
| U Iron binding capacity (UIBC)    | NS   | NS   | NS   | -42  | -31      | -462 | -85       | -91 | -76       | NS        |

|                                   |    |    |    |    |    |    |    |    |           |          |
|-----------------------------------|----|----|----|----|----|----|----|----|-----------|----------|
| Serum iron                        | NS | NS | NS | NS | NS | 17 | NS | 92 | NS        | NS       |
| U Gamma glutamyltransferase (GGT) | NS | NS | NS | NS | NS | NS | NS | NS | -138      | NS       |
| U LDH                             | NS | NS | NS | NS | NS | NS | NS | NS | 207       | 135 (91) |
| LDH/creatinine                    | NS | NS | NS | NS | NS | NS | NS | NS | 244 (114) | NS       |

Only statistically significant findings were listed in this table

**Bolded = treatment-related**

**NS= Not statistically significant**

**()=recovery**

### Urinalysis

- Test article-related urine parameter changes reported:
  - At doses  $\geq 0.1$  mg/kg/day was increased protein
  - At doses  $\geq 0.3$  mg/kg/day were increased urobilinogen and bilirubin
  - At 1 mg/kg/day was hyaline casts
- The following parameters persisted throughout recovery:
  - At doses  $\geq 0.1$  mg/kg/day, increased protein
  - At doses  $\geq 0.3$  mg/kg/day, increased urobilinogen
  - At 1 mg/kg/day, bilirubin

### Macroscopic Findings

- At doses  $\geq 0.3$  mg/kg/day included enlarged, dark, mottled and mass of the adrenal gland; distended bile duct, fluid lumen and material lumen of the liver; dark areas in mucosa of glandular region and distended of the stomach; thickened wall of the duodenum; gelatinous of the pancreas; soft and small testis; small epididymis and seminal vesicle; teeth missing and enlarged mandibular).
- At 1 mg/kg/day included thickened wall of the ileum; and enlarged, pale and mottled kidney)
- No macroscopic findings were reported at doses  $\leq 0.1$  mg/kg/day.
- At the end of the recovery period pale adrenal cortex (female) and pale kidney (female) persisted at 1 mg/kg/day.

### Organ Weights

- Test article-related increases in a number of relative organ weights were reported at doses  $\geq 0.01$  mg/kg/day.
  - At 1 mg/kg/day, there were test article-related increases in organ weights relative to body weight during the interim sacrifice in males (brain, liver, kidney, spleen, testis, thymus, salivary gland, adrenal, and epididymis) and females (brain, uterus, thymus, pituitary, salivary gland, ovary and adrenal).
    - At the end of the recovery period relative organ weight increases persisted at 1 mg/kg/day in males (increases in liver, lung, heart and

- salivary gland) and females (increases in liver, spleen, thymus, pituitary, salivary gland and thyroid).
- At 0.3 mg/kg/day there were test article-related increases in relative organ weights during the terminal sacrifice: In males (brain, liver, testis, thymus, lung, salivary gland, adrenal gland, thyroid and epididymis) and in females (brain, liver, spleen, uterus, thymus, heart, salivary gland, ovary and adrenal gland).
    - At the end of the recovery period at 0.3 mg/kg/day, relative organ weight increases persisted in males (kidney, testis, lung and salivary gland) and females (brain, spleen, heart, adrenal and salivary gland).
  - Test article-related changes in relative organ weights were reported at 0.1 mg/kg/day (male kidney, female brain and heart), 0.03 mg/kg/day (male kidney, female lung and brain) and at 0.01 mg/kg/day (male kidney).
    - No effects on relative organ weight were evident at the end of the recovery period at doses  $\leq 0.03$  mg/kg/day.

### Microscopic Findings

- Test article-related microscopic findings were reported at doses  $\geq 0.1$  mg/kg/day in both sexes. In general, the incidence and/or severity of the findings were dose dependent. By the end of the recovery period, a number of the microscopic findings were reported at doses  $\geq 0.1$  mg/kg/day.
  - ◆ At doses  $\geq 0.3$  mg/kg/day, severe test article-related microscopic findings were observed in the adrenal gland (moderate to severe - congestion/hemorrhage, moderate to marked-degeneration, marked to severe-necrosis), brain (slight to marked- vacuolated cells in choroid plexus, moderate - choroid vessel necrosis), kidney (moderate to marked - glomerulopathy, moderate to marked -chronic nephropathy), bone femur (marked to severe - hypertrophy of the physis and loss of the primary spongiosa), liver and bile ducts (minimal to marked - inflammation and biliary hypertrophy/hyperplasia), incisors (severe - degeneration of odontoblasts and marked - ameloblasts, marked to severe - dentin dysplasia), pancreas (marked- atrophy), duodenum (marked to severe - transmural and mucosal hypertrophy), ovary (moderate- atrophy and cyst follicle) and uterus (moderate - atrophy).
  - ◆ Other microscopic findings were reported with less pronounced effects: pituitary (minimal to marked - hypertrophic and degenerate chromophobe cells), stomach (slight - congestion, moderate - hyperplasia/metaplasia of fundic epithelium), heart (slight to minimal - focal necrosis, myofiber degeneration), lymphoid organs (marked - lymphoid depletion), adrenal medulla (minimal to severe necrosis) and bone marrow (minimal to marked - hypocellularity).
  - ◆ At 0.1 mg/kg/day, the test article-related microscopic findings reported were observed in the brain (slight vacuolated cells in choroid plexus, choroid vessel necrosis), bone femur (minimal hypertrophy of the physis and moderate - loss of the primary spongiosa), pituitary (slight - hypertrophic and degenerate chromophobe cells), adrenal cortex (slight degeneration of zona fasciculata, congestion/hemorrhage), liver (slight pigment,

hepatocytes, brown, granular, hypertrophy/hyperplasia, bile ducts), kidney (minimal-glomerulopathy), heart (minimal degeneration, focal inflammation).

**Microscopic Findings:**

| Incidence and severity of pronounced microscopic findings- interim and terminal sacrifice |            |            |                |            |                |          |               |            |               |            |               |            |
|-------------------------------------------------------------------------------------------|------------|------------|----------------|------------|----------------|----------|---------------|------------|---------------|------------|---------------|------------|
| Organ                                                                                     | Control    |            | 0.01 mg/kg/day |            | 0.03 mg/kg/day |          | 0.1 mg/kg/day |            | 0.3 mg/kg/day |            | 1.0 mg/kg/day |            |
| Sex:number/sex                                                                            | M:19       | F:20       | M:10           | F:10       | M:10           | F:10     | M:9           | F:10       | M:9           | F:10       | M:9           | F:10       |
| <b>Brain</b>                                                                              |            |            |                |            |                |          |               |            |               |            |               |            |
| Vacuolated cells, choroid plexus                                                          | 0          | 0          | 0              | 0          | 0              | 0        | 0             | 4<br>(1)   | 5<br>(1-2)    | 8<br>(1-2) | 9<br>(1-3)    | 9<br>(2-4) |
| Necrosis, fibrinoid, vessel, choroid plexus                                               | 0          | 0          | 0              | 0          | 0              | 0        | 0             | 0          | 1<br>(1)      | 3<br>(1-3) | 5<br>(1-2)    | 3<br>(2-3) |
| <b>Pituitary</b>                                                                          |            |            |                |            |                |          |               |            |               |            |               |            |
| Hypertrophy/ degeneration, chromophobes, pars distalis                                    | 0          | 0          | 0              | 0          | 0              | 0        | 3<br>(1)      | 0          | 3<br>(1)      | 0          | 1<br>(1)      | 9<br>(2-4) |
| <b>Adrenal Cortex</b>                                                                     |            |            |                |            |                |          |               |            |               |            |               |            |
| Degeneration, zona fasciculata                                                            | 0          | 0          | 0              | 0          | 0              | 0        | 1<br>(1)      | 0          | 4<br>(1-2)    | 6<br>(1-3) | 6<br>(2-4)    | 9<br>(1-4) |
| Necrosis                                                                                  | 0          | 0          | 0              | 0          | 0              | 0        | 0             | 0          | 5<br>(2-4)    | 8<br>(1-4) | 6<br>(1-5)    | 6<br>(3-4) |
| Congestion/ hemorrhage                                                                    | 0          | 0          | 0              | 0          | 0              | 1<br>(1) | 0             | 1<br>(1)   | 7<br>(1-3)    | 9<br>(2-4) | 10<br>(2-5)   | 9<br>(1-5) |
| <b>Adrenal Medulla</b>                                                                    |            |            |                |            |                |          |               |            |               |            |               |            |
| Necrosis                                                                                  | 0          | 0          | 0              | 0          | 0              | 0        | 0             | 0          | 3<br>(1)      | 4<br>(1)   | 0             | 4<br>(2-5) |
| <b>Heart</b>                                                                              |            |            |                |            |                |          |               |            |               |            |               |            |
| Necrosis                                                                                  | 0          | 0          | 0              | 0          | 0              | 0        | 0             | 0          | 0             | 0          | 0             | 2<br>(1)   |
| Degeneration                                                                              | 0          | 1<br>(1)   | 2<br>(1)       | 1<br>(1)   | 1<br>(1)       | 0        | 2<br>(1)      | 0          | 1<br>(1)      | 1<br>(1)   | 8<br>(1-2)    | 5<br>(1-2) |
| Inflammation, Focal                                                                       | 0          | 0          | 3<br>(1)       | 1<br>(1)   | 1<br>(2)       | 0        | 5<br>(1-2)    | 1<br>(2)   | 0             | 1<br>(2)   | 1<br>(1)      | 2<br>(1)   |
| <b>Liver</b>                                                                              |            |            |                |            |                |          |               |            |               |            |               |            |
| Pigment, hepatocytes/ Kupffer cells                                                       | 0          | 0          | 0              | 0          | 0              | 0        | 0             | 0          | 2<br>(2)      | 0          | 0             | 2<br>(1)   |
| Necrosis/inflammation, focal acute                                                        | 3<br>(1)   | 4<br>(1-2) | 2<br>(1)       | 9<br>(1-2) | 3<br>(1)       | 5<br>(1) | 0             | 0          | 0             | 2<br>(2)   | 0             | 1<br>(1)   |
| Hypertrophy/hyperplasia, bile ducts                                                       | 0          | 0          | 0              | 0          | 0              | 0        | 0             | 3<br>(1)   | 2<br>(3-4)    | 9<br>(1-3) | 4<br>(1-2)    | 1<br>(1)   |
| <b>Kidneys</b>                                                                            |            |            |                |            |                |          |               |            |               |            |               |            |
| Glomerulopathy                                                                            | 3<br>(1)   | 2<br>(1)   | 9<br>(1)       | 5<br>(1)   | 10<br>(1)      | 6<br>(1) | 10<br>(2)     | 9<br>(1-2) | 9<br>(3-4)    | 9<br>(2-3) | 10<br>(3-4)   | 9<br>(2-4) |
| Tubule, regeneration                                                                      | 4<br>(1-2) | 1<br>(1)   | 7<br>(1)       | 1<br>(1)   | 3<br>(1)       | 1<br>(1) | 9<br>(1-2)    | 2<br>(1)   | 8<br>(1-4)    | 4<br>(1)   | 9<br>(1-3)    | 8<br>(1-3) |
| <b>Stomach</b>                                                                            |            |            |                |            |                |          |               |            |               |            |               |            |
| Congestion                                                                                | 0          | 0          | 0              | 0          | 0              | 0        | 0             | 0          | 0             | 0          | 5<br>(1-2)    | 4<br>(1-2) |
| Hyperplasia/metaplasia, fundic epithelium                                                 | 0          | 0          | 0              | 0          | 0              | 0        | 0             | 0          | 0             | 0          | 8<br>(1-3)    | 2<br>(2-3) |
| <b>Duodenum</b>                                                                           |            |            |                |            |                |          |               |            |               |            |               |            |
| Hypertrophy, transmural/mucosa                                                            | 0          | 0          | 0              | 0          | 0              | 0        | 0             | 0          | 9<br>(2-4)    | 7<br>(1-3) | 9<br>(1-5)    | 6<br>(1-3) |

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|                                                                                                                                                     |          |          |   |   |   |   |          |             |            |             |             |             |            |
|-----------------------------------------------------------------------------------------------------------------------------------------------------|----------|----------|---|---|---|---|----------|-------------|------------|-------------|-------------|-------------|------------|
| Inflammation acute                                                                                                                                  | 0        | 0        | 0 | 0 | 0 | 0 | 0        | 0           | 0          | 1<br>(3)    | 3<br>(1-3)  | 3<br>(1-3)  |            |
| <b>Pancreas</b>                                                                                                                                     |          |          |   |   |   |   |          |             |            |             |             |             |            |
| Atrophy                                                                                                                                             | 1<br>(1) | 1<br>(1) | 0 | 0 | 0 | 0 | 0        | 0           | 0          | 5<br>(1-4)  | 5<br>(1-3)  | 10<br>(1-4) | 7<br>(1-3) |
| <b>Thymus</b>                                                                                                                                       |          |          |   |   |   |   |          |             |            |             |             |             |            |
| Atrophy                                                                                                                                             | 0        | 0        | 0 | 0 | 0 | 0 | 0        | 0           | 0          | 3<br>(1-4)  | 3<br>(1-4)  | 3<br>(1-4)  | 2<br>(1-2) |
| <b>Bone femur</b>                                                                                                                                   |          |          |   |   |   |   |          |             |            |             |             |             |            |
| Hypertrophy of the physis                                                                                                                           | 0        | 0        | 0 | 0 | 0 | 0 | 2<br>(1) | 1<br>(1)    | 8<br>(1-3) | 10<br>(1-4) | 10<br>(3-4) | 9<br>(3-5)  |            |
| Loss of the primary spongiosa                                                                                                                       | 0        | 0        | 0 | 0 | 0 | 0 | 2<br>(1) | 10<br>(1-3) | 6<br>(2-4) | 10<br>(1-5) | 10<br>(4-5) | 9<br>(3)    |            |
| Hypertrophy, articular cartilage                                                                                                                    | 0        | 0        | 0 | 0 | 0 | 0 | 0        | 0           | 3<br>(1)   | 8<br>(1-2)  | 5<br>(1-3)  | 8<br>(3)    |            |
| <b>Teeth incisors</b>                                                                                                                               |          |          |   |   |   |   |          |             |            |             |             |             |            |
| Degeneration of odontoblasts                                                                                                                        | 0        | 0        | 0 | 0 | 0 | 0 | 0        | 0           | 6<br>(1-5) | 10<br>(4-5) | 9<br>(4)    | 9<br>(2-5)  |            |
| Degeneration of ameloblasts                                                                                                                         | 0        | 0        | 0 | 0 | 0 | 0 | 0        | 0           | 4<br>(1-4) | 10<br>(3-4) | 8<br>(1-3)  | 9<br>(1-4)  |            |
| Dentin dysplasia                                                                                                                                    | 0        | 0        | 0 | 0 | 0 | 0 | 0        | 0           | 6<br>(2-5) | 10<br>(4-5) | 9<br>(3-4)  | 9<br>(2-4)  |            |
| <b>Ovary</b>                                                                                                                                        |          |          |   |   |   |   |          |             |            |             |             |             |            |
| Atrophy and cyst follicle                                                                                                                           | -        | 0        | - | 0 | - | 0 | -        | 0           | -          | 10<br>(1-3) | -           | 10<br>(1-3) |            |
| <b>Uterus</b>                                                                                                                                       |          |          |   |   |   |   |          |             |            |             |             |             |            |
| Atrophy                                                                                                                                             | -        | 0        | - | 0 | - | 0 | -        | 0           | -          | 10<br>(1-3) | -           | 10<br>(1-3) |            |
| <b>Bone marrow (femur and sternum)</b>                                                                                                              |          |          |   |   |   |   |          |             |            |             |             |             |            |
| Hypocellularity                                                                                                                                     | 0        | 0        | 0 | 0 | 0 | 0 | 0        | 0           | 4<br>(1)   | 3<br>(1)    | 10<br>(1-4) | 8<br>(1-3)  |            |
| ( )= severity grade range                                                                                                                           |          |          |   |   |   |   |          |             |            |             |             |             |            |
| <b>Grades for Severity of the microscopic findings:</b>                                                                                             |          |          |   |   |   |   |          |             |            |             |             |             |            |
| 1 Minimal - the least amount of change observed with the light microscope                                                                           |          |          |   |   |   |   |          |             |            |             |             |             |            |
| 2 Slight - less than average amount of change, but readily discernible as abnormal                                                                  |          |          |   |   |   |   |          |             |            |             |             |             |            |
| 3 Moderate - the average amount of change expected for a lesion                                                                                     |          |          |   |   |   |   |          |             |            |             |             |             |            |
| 4 Marked - a marked amount of change with possible loss of function of the affected cells or organs                                                 |          |          |   |   |   |   |          |             |            |             |             |             |            |
| 5 Severe - a great amount of change with probable loss of function of the affected cell or organs and frequently involves large areas of the organ. |          |          |   |   |   |   |          |             |            |             |             |             |            |

Recovery period:

- At 1 mg/kg/day, microscopic findings at the end of recovery were observed in the brain (minimal to slight - vacuolated cells, choroid plexus), adrenal cortex (minimal to slight - degeneration, congestion/hemorrhage), heart (slight to moderate - degeneration), kidney (minimal to severe - glomerulopathy, casts, tubules, protein (hyaline), nephropathy, chronic); minimal hypocellular bone marrow (sternum, femur), , bone (minimal-Hypertrophy of the physis and minimal to marked -Loss of the primary spongiosa), pancreas (minimal - infiltrate, interstitial, macrophage, atrophy), ovary (minimal - atrophy), uterus (slight - atrophy) and teeth incisors and molar (slight to marked - hyperplasia, odontoblasts, dysplasia/degeneration and dentin).
- At 0.3 mg/kg/day, microscopic findings reported at the end of the recovery period were observed in the adrenal cortex (moderate to marked - atrophy, pigment, hemosiderin) and duodenum (minimal to moderate - hypertrophy, transmural).
- At 0.1 and 0.3 mg/kg/day, microscopic findings at the end of the recovery period were reported in the brain (slight - vacuolated cells, choroid plexus), heart (minimal to slight - degeneration, focal inflammation), liver (minimal to moderate - hepatocytes, hypertrophy/hyperplasia, bile ducts); kidney (slight to moderate - glomerulopathy, casts, tubules, protein (hyaline), nephropathy, chronic), pancreas (slight - atrophy, focal infiltrate mononuclear cell, inflammation), bone (minimal-Hypertrophy of the physis and minimal to marked -loss of the primary spongiosa), hypertrophy bone marrow (femur) and uterus (slight to moderate- dilatation).

*Microscopic Findings – Recovery:*

| <b>Recovery: Incidence and severity of predominant microscopic findings at interim and terminal recovery</b> |         |            |               |          |               |          |               |            |
|--------------------------------------------------------------------------------------------------------------|---------|------------|---------------|----------|---------------|----------|---------------|------------|
| Organ                                                                                                        | control |            | 0.1 mg/kg/day |          | 0.3 mg/kg/day |          | 1.0 mg/kg/day |            |
| Sex/n                                                                                                        | M:10    | F:10       | M:5           | F:5      | M:3           | F:3      | M:3           | F:3        |
| <b>Brain</b>                                                                                                 |         |            |               |          |               |          |               |            |
| Vacuolated cells, choroid plexus                                                                             | 0       | 0          | 1<br>(1)      | 0        | 2<br>(1)      | 0        | 0             | 2<br>(1-2) |
| <b>Adrenal Cortex</b>                                                                                        |         |            |               |          |               |          |               |            |
| Degeneration, zona fasciculata                                                                               | 0       | 0          | 0             | 1<br>(2) | 0             | 0        | 2<br>(1-2)    | 2<br>(1-2) |
| Congestion/hemorrhage                                                                                        | 0       | 0          | 0             | 0        | 0             | 0        | 1<br>(2)      | 2<br>(2)   |
| Pigment, hemosiderin                                                                                         | 0       | 0          | 0             | 0        | 1<br>(4)      | 0        | 0             | 0          |
| Hypertrophy                                                                                                  | 0       | 0          | 0             | 0        | 0             | 1<br>(1) | 0             | 0          |
| Atrophy                                                                                                      | 0       | 0          | 0             | 0        | 1 (3)         | 0        | 0             | 0          |
| <b>Heart</b>                                                                                                 |         |            |               |          |               |          |               |            |
| Necrosis                                                                                                     | 0       | 0          | 0             | 0        | 0             | 0        | 0             | 0          |
| Degeneration                                                                                                 | 0       | 0          | 1<br>(1)      | 0        | 0             | 0        | 0             | 2<br>(2-3) |
| Inflammation, Focal                                                                                          | 0       | 0          | 1<br>(1)      | 0        | 1<br>(2)      | 0        | 0             | 0          |
| <b>Liver</b>                                                                                                 |         |            |               |          |               |          |               |            |
| Infiltration, mononuclear/eosinophils                                                                        | 0       | T 5<br>(1) | 1<br>(2)      | 2<br>(1) | 1<br>(1)      | 2<br>(1) | 0             | 1<br>(2)   |

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|                                            |            |              |            |            |            |            |            |            |
|--------------------------------------------|------------|--------------|------------|------------|------------|------------|------------|------------|
| Hypertrophy, hepatocytes                   | 0          | 1<br>(1)     | 4<br>(1-2) | 1<br>(1)   | 3<br>(2)   | 0          | 0          | 0          |
| Necrosis/inflammation, focal acute         | 0          | T 5<br>(1-2) | 5<br>(1)   | 3<br>(1)   | 2<br>(3)   | 2<br>(1-2) | 0          | 0          |
| Hypertrophy/hyperplasia, bile ducts        | 0          | 0            | 2<br>(1)   | 1<br>(1)   | 1<br>(1)   | 2<br>(3)   | 0          | 0          |
| Chronic inflammation, bile duct            | 0          | 0            | 0          | 0          | 2<br>(3)   | 1<br>(4)   | 0          | 0          |
| <b>Kidneys</b>                             |            |              |            |            |            |            |            |            |
| Glomerulopathy                             | 0          | T 4<br>(1)   | 4<br>(2-3) | 4<br>(1-2) | 3<br>(1-3) | 3<br>(2)   | 3<br>(1-2) | 3<br>(1-5) |
| Casts, tubule, protein (hyaline)           | 0          | 0            | 1<br>(1)   | 1<br>(2)   | 2<br>(1-2) | 0          | 2<br>(1-2) | 1<br>(3)   |
| Nephropathy, chronic                       | 0          | 0            | 0          | 0          | 0          | 0          | 0          | 3<br>(1-4) |
| Pigment, brown, proximal tubule epithelium | 0          | 0            | 0          | 0          | 0          | 0          | 0          | 1<br>(2)   |
| Tubule regeneration                        | 0          | T 3<br>(1)   | 5<br>(1-3) | 2<br>(1)   | 2<br>(3)   | 0          | 0          | 0          |
| Inflammation, focal, mononuclear cell      | 0          | T 2<br>(1)   | 0          | 2<br>(1)   | 0          | 1<br>(1)   | 0          | 0          |
| Tubule mineralization                      | 0          | 2<br>(1-2)   | 0          | 2<br>(1)   | 0          | 2<br>(1-2) | 0          | 0          |
| <b>Duodenum</b>                            |            |              |            |            |            |            |            |            |
| Hypertrophy, transmural/mucosa             | 0          | 0            | 0          | 0          | 1<br>(1)   | 2<br>(1-3) | 0          | 0          |
| Inflammation acute                         | 0          | 0            | 0          | 0          | 0          | 0          | 0          | 0          |
| <b>Pancreas</b>                            |            |              |            |            |            |            |            |            |
| Infiltrate, interstitial, macrophage       | T 1<br>(1) | T 1<br>(1-2) | 1<br>(1)   | 0          | 0          | 0          | 0          | 3<br>(1)   |
| Atrophy                                    | 0          | 0            | 0          | 0          | 1<br>(1)   | 1<br>(2)   | 0          | 1<br>(1)   |
| Inflammation                               | 0          | 0            | 0          | 0          | 1<br>(1)   | 0          | 0          | 0          |
| <b>Bone femur</b>                          |            |              |            |            |            |            |            |            |
| Hypertrophy of the physis                  | 0          | 0            | 0          | 0          | 1<br>(1)   | 1<br>(1)   | 0          | 2<br>(1)   |
| Loss of the primary spongiosa              | 0          | 0            | 1<br>(1)   | 0          | 1<br>(4)   | 1<br>(1)   | 0          | 3<br>(1-4) |
| <b>Teeth incisors</b>                      |            |              |            |            |            |            |            |            |
| Hyperplasia of odontoblasts                | 0          | 0            | 0          | 0          | 0          | 0          | 2<br>(3)   | 0          |
| Degeneration of ameloblasts                | 0          | 0            | 0          | 0          | 0          | 0          | 0          | 0          |
| Dentin dysplasia                           | 0          | 0            | 0          | 0          | 0          | 0          | 3<br>(3-4) | 1<br>(2)   |
| <b>Teeth Molar</b>                         |            |              |            |            |            |            |            |            |
| Dysplasia /Degeneration dentin             | 0          | 0            | 0          | 0          | 0          | 0          | 0          | 2<br>(1-2) |
| <b>Ovary</b>                               |            |              |            |            |            |            |            |            |
| Atrophy and cyst follicle                  | -          | 0            | -          | 1<br>(3)   | -          | 0          | -          | 1<br>(1)   |
| <b>Uterus</b>                              |            |              |            |            |            |            |            |            |
| Atrophy                                    | -          | 0            | -          | 0          | -          | 0          | -          | 1<br>(2)   |
| Dilatation                                 | -          | 0            | -          | 1<br>(2)   | -          | 1<br>(3)   | -          | 0          |

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |   |   |   |   |   |   |   |   |          |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---|---|---|---|---|---|---|---|----------|
| <b>Bone marrow (femur and sternum)</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |   |   |   |   |   |   |   |   |          |
| Hypocellularity                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1<br>(1) |
| <b>( ) = severity grade</b><br><b>Grades for Severity of the microscopic findings:</b><br>1 Minimal - the least amount of change observed with the light microscope<br>2 Slight - less than average amount of change, but readily discernible as abnormal<br>3 Moderate - the average amount of change expected for a lesion<br>4 Marked - a marked amount of change with possible loss of function of the affected cells or organs<br>5 Severe - a great amount of change with probable loss of function of the affected cell or organs and frequently involves large areas of the organ<br>T-terminal recovery |   |   |   |   |   |   |   |   |          |

**Conclusion**

The NOAEL was considered to be 0.03 mg/kg/day (HED = 0.29g/day, or 0.2X the recommended human dose) based on adverse microscopic findings. Toxicities at  $\geq 0.3$ mg/kg/day were significant and many were not recoverable. Partial recovery of most effects was reported at doses  $\geq 0.1$  mg/kg/day, although renal effects were not recoverable at these doses.

| <b>Study title: KRN951: A 26-Week Oral Toxicity Study in Rats With a 6-Week Recovery Period</b> |                                                              |
|-------------------------------------------------------------------------------------------------|--------------------------------------------------------------|
| Study no.:                                                                                      | 1458-005                                                     |
| Sponsor:                                                                                        | AVEO Pharmaceuticals, Inc.<br>Cambridge, Massachusetts 02139 |
| Conducting laboratory and location:                                                             | (b) (4)                                                      |
| Date of study initiation:                                                                       | 23 October, 2008                                             |
| GLP compliance and QA statement:                                                                | Yes                                                          |
| Drug, lot #, and % purity:                                                                      | AV-951, CDM-005 and 99.53%                                   |

**Key Findings**

- No test article-related mortalities were reported.
- The only test article-related clinical observation reported was white teeth at doses  $\geq 0.005$  mg/kg/day. The effect was not considered to be an adverse effect.
- Female body weights at 0.08 mg/kg/day, were slightly decreased (up to 6%) during the last 3 weeks of treatment. The effect was not considered to be an adverse effect.
- Test article-related increases in leukocytes, hemoglobin, hematocrit and erythrocytes were reported in male and female rats at 0.08 mg/kg/day at weeks 13 and/or 26. These findings were not considered to be adverse.
- Test article-related decreases were reported at 0.08 mg/kg/day in total protein, albumin and globulin in both sexes at week 13 and 26. These findings were not considered to be adverse, due to the magnitude of effect.
- There were no test article-related effects on organ weights, macroscopic and microscopic findings at all dose levels.
- No test article-related effects were reported at the end of the recovery period.

- The NOAEL was established to be the highest dose tested, 0.08 mg/kg/day (HED = 0.78g/day; or 0.5-fold the maximum recommended human dose).

**Methods:**

Doses/  
 Number/Sex/Group:

**Table 1. Study Design**

| Treatment group | Dose level (mg/kg/day) | Number of animals       |        |                             |                 |
|-----------------|------------------------|-------------------------|--------|-----------------------------|-----------------|
|                 |                        | Main study <sup>a</sup> |        | Toxicokinetics <sup>b</sup> |                 |
|                 |                        | Male                    | Female | Male                        | Female          |
| 1               | Vehicle control        | 25                      | 25     | -                           | -               |
| 2               | 0.005                  | 25                      | 25     | -                           | -               |
| 3               | 0.02                   | 25                      | 25     | -                           | -               |
| 4               | 0.08                   | 25                      | 25     | -                           | -               |
| 5               | Vehicle control        | -                       | -      | 11 <sup>c</sup>             | 11 <sup>c</sup> |
| 6               | 0.005                  | -                       | -      | 11                          | 11              |
| 7               | 0.02                   | -                       | -      | 11                          | 11              |
| 8               | 0.08                   | -                       | -      | 11                          | 11              |

<sup>a</sup> At the end of the 26-Week administration period, the last 5 surviving animals/sex/group were placed in a 6-week recovery.

<sup>b</sup> Two additional animals/sex/treatment group were included as replacement animals.

<sup>c</sup> Vehicle control group was decreased to 5/sex on Day 3.

*(excerpted from Applicant's report)*

Frequency of dosing: Daily for up to 182 days.  
 Route of administration: Oral gavage  
 Dose volume: 10 mL/kg  
 Formulation/Vehicle: Vehicle, 0.5% methylcellulose  
 Sex/Species/Strain: Naïve male and female Crl:CD®(SD) rats  
 Age: Approximately 6 weeks of age  
 Weight: 243 to 297 g for males  
 182 to 218 g for females.  
 Toxicokinetic evaluation: Blood samples were obtained from 3 animals/sex/group at one hour post-dose on days 1, 91 and 182 (Group 5; vehicle control). Blood samples were obtained from 3 animals/sex/group at pre-dose and at 0.5, 1, 2, 4, 8, 16 and 24 hours post-dose on days 1, 91 and 182 (Groups 6 – 8).  
 Endpoints evaluated: Mortality, clinical observations, cage side observations, ophthalmic examinations, body weight, food consumption, clinical pathology (samples were taken on week 13, prior to terminal necropsy and prior to recovery), immunology evaluation, macro and microscopic evaluation and organ weights.  
 Termination and necropsy: At the end of the 26 weeks of administration (terminal necropsy), 5 animals per sex were maintained for a 6-week recovery period for each group (recovery necropsy). Histopathology evaluations were performed at all dose groups.  
 Deviation from study protocol: None of the deviations affected the integrity or interpretability of the results of the study.

**Results:**

**Analysis of dosing formulations**

The reported data indicated that the formulations were stable (up to 21 days) and homogenous. Analyses were performed and confirmed that formulation concentrations during weeks 1, 2, 4, 8, 16, 20, and 24, were within the acceptable range ( $\pm 15\%$ ) with the exception of the formulation on week 3 (18.7%) and 12 (16.8%).

**Mortality**

No test article-related mortalities were reported. Two male rats at 0.005 mg/kg/day and one male rat at 0.08 mg/kg/day were found dead or moribund sacrificed. The reported mortalities were not considered test article-related. One male rat was inadvertently killed as the technician was closing the cage on Day 89 (male at 0.08 mg/kg/day), the second male rat (0.005 mg/kg/day) was euthanized due to the severe clinical observations and the cause of death was the formation of multicentric malignant lymphoma; and the cause of death for the third male (0.005 mg/kg/day) is unknown. Due to lack of dose response relationship the deaths at 0.005 mg/kg/day were not considered test article-related.

**Mortalities:**

| Dose (mg/kg/day) | Sex  | Day of moribund sacrifice | Day of found dead | Cause of death and other comments                                                                                                             |
|------------------|------|---------------------------|-------------------|-----------------------------------------------------------------------------------------------------------------------------------------------|
| 0.005 (main)     | Male | 82                        | -                 | The cause of death was not considered to be test article related. The death was a result of the formation of multicentric malignant lymphoma. |
| 0.08 (main)      | Male | 89                        | -                 | Rat was killed accidentally. Technician closed cage on animal.                                                                                |
| 0.005 (TK)       | Male | -                         | 32                | Necropsy was not performed and cause of death was not determined                                                                              |
| Control*         | Male | -                         | during week       | Rats were found dead or euthanized due to moribund condition. Animals were replaced.                                                          |
| 0.08 (TK)*       | Male | -                         |                   |                                                                                                                                               |
| 0.08 (TK)*       | Male | -                         |                   |                                                                                                                                               |

\* One main study male vehicle control animal (number 1022), and two toxicokinetics (TK) males at 0.08 mg/kg/day (animal numbers 1136 and 1137) were found dead or euthanized due to moribund condition during the first 6 days of the study and were replaced. Data from these animals were not reported, however, data was maintained in the study file.

- = not applicable

**Clinical Signs**

The only test article-related clinical observation was white teeth at doses  $\geq 0.005$  mg/kg/day. The observation was evident in male and female rats at all dose groups and lasted up to 14 weeks. The observation was noted in a small number of animals per group. The reported observation was evident in all dose groups and was consistent with findings in prior study (13-week repeat dose study in rats-study # 6691-158); therefore, the effect was considered to be test article-related.

No test article-related observations were reported at the end of the recovery period.

**Clinical Observations - Number of observations per group**

| Dose (mg/kg/day)                                | M    | F    | M     | F     | M    | F    | M    | F    |
|-------------------------------------------------|------|------|-------|-------|------|------|------|------|
|                                                 | Cont | Cont | 0.005 | 0.005 | 0.02 | 0.02 | 0.08 | 0.08 |
| Teeth discolored – white (one or both incisors) | 0    | 1    | 4     | 2     | 1    | 2    | 6    | 1    |

Cont = control

**Body Weights**

There were no test article-related effects on male body weights reported throughout the treatment period. Females body weights at 0.08 mg/kg/day were slightly decreased (up to 6%) during the last 3 weeks of treatment. This finding was not considered to be an adverse finding. No effects on body weights were reported at the end of the recovery period in both sexes.

**Mean Body Weights:**

| Summary of Group Mean Body Weights in Grams |                        |         |        |         |        |
|---------------------------------------------|------------------------|---------|--------|---------|--------|
| Main Study                                  |                        |         |        |         |        |
| Group Number                                | Dose Level (mg/kg/day) | Male    |        | Female  |        |
|                                             |                        | Week 26 | (%)    | Week 26 | (%)    |
| 1                                           | 0                      | 601.8   | -      | 367.6   | -      |
| 2                                           | 0.005                  | 610.8   | (+1.5) | 362.6   | (-1.4) |
| 3                                           | 0.02                   | 615.6   | (+2.3) | 361.4   | (-1.7) |
| 4                                           | 0.08                   | 598.4   | (-0.6) | 347.0   | (-5.6) |

(%) Percent difference from Control

(excerpted from Applicant's report)

**Food Consumption**

There were no test article-related effects on food consumption in male and female rats throughout the treatment period.

**Ophthalmoscopy**

There were no test article-related effects reported at all dose groups.

**Clinical Pathology**

**Hematology**

Test article-related increases in leukocytes, hemoglobin, hematocrit and erythrocytes were reported in male and female rats at 0.08 mg/kg/day at weeks 13 and/or 26. The findings are consistent with findings from prior study (13-week repeat dose study in rats-study # 6691-158).

However, these findings were not considered to be adverse effects due to the magnitude of effect.

No test article-related findings were reported at the end of the recovery period.

**Hematology (% change):**

| Dose (mg/kg/day) /Sex | M     | F     | M    | F    | M                 | F                   |
|-----------------------|-------|-------|------|------|-------------------|---------------------|
|                       | 0.005 | 0.005 | 0.02 | 0.02 | 0.08              | 0.08                |
| Leukocytes            | NS    | NS    | NS   | NS   | 25 (wk13)         | 48 (wk13)<br>69 (T) |
| Hemoglobin            | NS    | NS    | NS   | NS   | 6 (wk13)<br>8 (T) | 6 (wk13)<br>5 (T)   |
| Hematocrit            | NS    | NS    | NS   | NS   | 7 (T)             | 5 (T)               |
| Erythrocytes          | NS    | NS    | NS   | NS   | NS                | 5 (T)               |

*Only statistically significant findings were listed in this table*

*NS= Not statistically significant*

*(T)=terminal sacrifice*

*(wk13) = week 13*

*Coagulation*

There were no test article-related effects reported at all dose levels.

*Clinical Chemistry*

Test article-related decreases were reported at 0.08 mg/kg/day in total protein, albumin and globulin in both sexes at week 13 and 26. The findings are consistent with findings from prior study (13-week repeat dose study in rats-study # 6691-158). However, these findings were not considered to be adverse effects due to the magnitude of effect.

There were no test article-related findings reported at the end of the recovery period.

**Clinical Chemistry (% change):**

| Dose<br>(mg/kg/day)<br>/Sex | M            | F     | M            | F         | M                     | F                     |
|-----------------------------|--------------|-------|--------------|-----------|-----------------------|-----------------------|
|                             | 0.005        | 0.005 | 0.02         | 0.02      | 0.08                  | 0.08                  |
| Phosphorus                  | NS           | NS    | NS           | NS        | NS                    | -14 (R)               |
| ALT                         | 17<br>(wk13) |       | 22<br>(wk13) | 70 (wk13) | NS                    | NS                    |
| AST                         | NS           | NS    | NS           | 68 (wk13) | NS                    | NS                    |
| Urea                        | NS           | NS    | NS           | NS        | NS                    | 13 (T)                |
| Nitrogen                    | 10 (T)       | NS    | NS           | NS        | 10 (T)                | NS                    |
| Total protein               | NS           | NS    | NS           | NS        | -12 (wk13)<br>-13 (T) | -10 (wk13)<br>-13 (T) |
| Albumin                     | NS           | NS    | NS           | NS        | -10 (wk13)<br>-10 (T) | -9 (wk13)<br>-10 (T)  |
| Globulin                    | NS           | NS    | NS           | NS        | -13 (wk13)<br>-17 (T) | -11 (wk13)<br>-16 (T) |
| Albumin/globulin            | NS           | NS    |              | 10 (R)    | 8 (T)                 | 9 (T)                 |
| TIBC                        | NS           | NS    | NS           | NS        | -12 (wk13)            | NS                    |

NS= Not statistically significant  
 (T)=terminal sacrifice  
 (wk13)= week 13  
 (R)=recovery

*Transferrin*

There were no test article-related effects on transferrin reported at all dose levels.

*Urinalysis*

There were no test article-related effects reported at all dose levels.

**Macroscopic Observations**

There were no test article-related effects reported at all dose levels.

*Organ weights*

The reported changes in organ weights are listed below. In general the changes were statistically significant, but of modest magnitude. Additionally, they were not correlated with macro and/or microscopic findings. As such, the toxicological significance of these changes is unknown.

**Organ Weights (% change):**

| Dose<br>(mg/kg/day)<br>/Sex | M     | F     | M      | F       | M                  | F       |
|-----------------------------|-------|-------|--------|---------|--------------------|---------|
|                             | 0.005 | 0.005 | 0.02   | 0.02    | 0.08               | 0.08    |
| Heart                       | NS    | NS    | -7 (r) | NS      | -10 (a)<br>-11 (r) | -13 (a) |
| Kidneys                     | NS    | NS    | -8 (r) | NS      | -9 (a)<br>-10 (r)  | NS      |
| Lung                        | NS    | NS    | NS     | -14 (r) | NS                 | -9 (a)  |
| Pituitary gland             | NS    | NS    | NS     | NS      | NS                 | -17 (a) |

*Only statistically significant and biologically meaningful findings were listed in this table*

*NS= Not statistically significant*

*(a)=absolute; (r)=organ weight/body weight*

**Microscopic Observations**

There were no test article-related effects reported at all dose levels.

No histopathology peer review was performed.

**Toxicokinetics**

- The toxicokinetic parameters were similar in male and female rats on days 1, 91 and 182.
- AUC<sub>0-24</sub>, C<sub>max</sub> and t<sub>1/2</sub> were higher on days 91 and 182 than on day 1, but were similar on days 91 and 182.
- AUC<sub>0-24</sub> was 1.8 to 2.6 times higher on days 91 and 182 than on day 1, indicating accumulation.
- C<sub>max</sub> was 1.6 to 2.9 times higher on days 91 and 182 than on day 1, indicating accumulation.
- The similarity in systemic exposure on days 91 and 182 suggests that steady state levels were reached by day 91, and that no further accumulation occurred beyond day 91.
- AUC<sub>0-24</sub> and C<sub>max</sub> increased in approximate proportion to dose on days 1, 91 and 182, suggesting that systemic exposure was linear with dose.
- T<sub>max</sub> was unaffected by dose level or duration of treatment. The rate of absorption (T<sub>max</sub>) ranged from 2 to 4 hours.
- Elimination half-life (t<sub>1/2</sub>) ranged from 9 to 45 hours.

**Toxicokinetics:**

**Table 2. Toxicokinetic Parameters for AV-951 in Male and Female Rats given Oral Doses**

| Day | Dose (mg/kg/day) | Sex | AUC <sub>0-24</sub> (hr·ng/mL) | AUC <sub>0-24</sub> /Dose ((hr·ng/mL)/mg/kg) | C <sub>max</sub> (ng/mL) | C <sub>max</sub> /Dose ((ng/mL)/mg/kg) | t <sub>1/2</sub> (hr) | T <sub>max</sub> (hr) |
|-----|------------------|-----|--------------------------------|----------------------------------------------|--------------------------|----------------------------------------|-----------------------|-----------------------|
| 1   | 0.005            | M   | 103                            | 20600                                        | 6.54                     | 1310                                   | 9.43                  | 4.00                  |
|     |                  | F   | 105                            | 21000                                        | 6.39                     | 1280                                   | 14.2                  | 4.00                  |
|     | 0.02             | M   | 371                            | 18500                                        | 24.3                     | 1220                                   | 9.49                  | 4.00                  |
|     |                  | F   | 422                            | 21100                                        | 25.5                     | 1280                                   | 9.87                  | 2.00                  |
|     | 0.08             | M   | 1830                           | 22900                                        | 127                      | 1590                                   | 9.23                  | 4.00                  |
|     |                  | F   | 1720                           | 21500                                        | 114                      | 1430                                   | 10.0                  | 8.00                  |
| 91  | 0.005            | M   | 266                            | 53200                                        | 15.7                     | 3130                                   | 32.2                  | 2.00                  |
|     |                  | F   | 262                            | 52400                                        | 14.2                     | 2830                                   | 45.1                  | 4.00                  |
|     | 0.02             | M   | 787                            | 39400                                        | 47.8                     | 2390                                   | 16.1                  | 4.00                  |
|     |                  | F   | 957                            | 47800                                        | 66.0                     | 3300                                   | 16.6                  | 2.00                  |
|     | 0.08             | M   | 3340                           | 41700                                        | 210                      | 2630                                   | 40.8                  | 4.00                  |
|     |                  | F   | 3880                           | 48500                                        | 248                      | 3100                                   | 15.9                  | 4.00                  |
| 182 | 0.005            | M   | 247                            | 49500                                        | 15.6                     | 3110                                   | 23.9                  | 2.00                  |
|     |                  | F   | 259                            | 51700                                        | 15.2                     | 3040                                   | 24.5                  | 4.00                  |
|     | 0.02             | M   | 852                            | 42600                                        | 60.9                     | 3050                                   | 13.3                  | 4.00                  |
|     |                  | F   | 895                            | 44800                                        | 74.6                     | 3730                                   | 18.2                  | 2.00                  |
|     | 0.08             | M   | 3700                           | 46300                                        | 249                      | 3120                                   | 16.7                  | 4.00                  |
|     |                  | F   | 4170                           | 52200                                        | 265                      | 3310                                   | 24.3                  | 4.00                  |

(excerpted from Applicant's report)

**Conclusion:**

There were minimal toxicities observed at all doses up to the highest dose tested (0.08 mg/kg/day). The clinical observation of white teeth was evident at all doses. Test article-related findings were evident at 0.08 mg/kg/day and included decrease in body weight, and hematological and clinical chemistry changes. The above observed effects were not considered to be adverse, and no test article-related macroscopic or microscopic findings were reported at any dose levels. The NOAEL was established to be the highest dose tested 0.08 mg/kg/day (0.5-fold the maximum recommended human dose).

Overall this repeat-dose toxicity study was insufficient, as the highest dose(s) assessed produced limited toxicity and dose-response relationships could not be evaluated. Given the low safety margin noted for this study in regard to the clinical dose, it is uncertain why the Applicant did not explore a more robust range of doses in this study. Given the lack of substantial toxicity in this study, the Applicant proposed to use the data from the 13-week rat study to inform the package insert regarding toxicities observed in rats.

**Title: 13-Week Gavage Toxicity and Toxicokinetic Study with a 5-Week Recovery Period with KRN951 in Cynomolgus Monkeys**

**Study # 6691-159**

|                                     |                                                              |
|-------------------------------------|--------------------------------------------------------------|
| Sponsor:                            | AVEO Pharmaceuticals, Inc.<br>Cambridge, Massachusetts 02139 |
| Conducting laboratory and location: | (b) (4)                                                      |
| Date of study initiation:           | 10 December 2003                                             |
| GLP compliance/QA statement:        | Yes                                                          |
| Drug, lot #, and % purity:          | KRN951, CDM-001 and 98.8%                                    |

### Key Findings

- The NOAEL was established to be 0.1 mg/kg/day (1.3-fold the maximum recommended human dose).
- No unscheduled **deaths** were reported at all dose levels.
- Dose of 1 mg/kg/day resulted in severe **clinical signs** that resulted in cessation of dosing after 4 weeks of dosing. The clinical signs included dehydrated appearance, hunched posture, thin appearance, hypoactivity, discolored, few/no,/non-formed feces, low/no food consumption. In general, the observations were more pronounced in males. At doses  $\geq$  0.1 mg/kg/day, low/no food consumption was observed and at 0.3 mg/kg/day dehydration and hunched appearance were observed in one male monkey. No remarkable clinical observations were reported during the recovery period.
- Mean **body weights** were decreased by up to 20% and 8% in males and females at 1 mg/kg/day, respectively, and by 18% and 8% in males and females at 0.3 mg/kg/day, respectively, during treatment period. No body weight changes were reported at the end of the recovery period.
- Test article-related **hematological changes** were evident at 1 mg/kg/day (increases in RBC parameters, fibrin and M/E ratio; decreases in WBC, RETIC, NEUT, MCV and PT). No hematological changes were reported at the end of the recovery period. No test article-related effects were reported at doses  $\leq$  0.3 mg/kg/day.
- Test article-related **clinical and urine chemistry** changes were evident at 1 mg/kg/day (increases in CK, SELA- $\alpha$  &  $\beta$ , iron, phospholipids; decreases in ALP, SDH, total bile acid, amylase, UIBC, U LDH, U creatinine). The clinical chemistry changes reported at doses  $\geq$  0.1 mg/kg/day (increases in SELA- $\alpha$ , CK, and phospholipids) were considered test article-related, but changes were of lesser magnitude. Other changes at doses  $\geq$  0.1 mg/kg/day were attributed to the reported decreases in food consumption and/or lower body weights. No changes were reported at the end of the recovery period.
- At doses  $\geq$  0.3 mg/kg/day, **organ weight changes** included significant decreases in absolute and relative thymus weights.
- Test article-related **macroscopic observations** were reported at 1 mg/kg/day (dark thyroid, dark adrenals, distended gallbladder and thickened gastric mucosa and/or dark areas on the gastric mucosa in the stomach of males). The findings in the thyroid and thymus (females) were evident at the end of the recovery period.

- Predominant test article-related **microscopic findings** included:
  - At  $\geq 0.3$  mg/kg/day effects in the following tissues were reported: bone (femur and tibia), gastric system (stomach, duodenum and pancreas), reproductive system (ovary and corpora lutea), adrenal cortex, lymphoid depletion of lymphoid organs (thymus, lymph nodes and spleen) and brain.
  - At  $\geq 0.1$  mg/kg/day in the following organs: brain and adrenal cortex.
  - The majority of the microscopic findings were recoverable after a 2-week recovery period at 1mg/kg. All of the findings at 0.1 and 0.3 mg/kg/day were recoverable during the 5-week recovery period.
  - No test article-related microscopic findings were reported at doses  $\leq 0.03$  mg/kg/day.
- Exposure to KRN951 increased with dose in both sexes. No gender differences were reported.  $C_{max}$  and AUC values were higher on days 28 and 91 than day 1, indicating accumulation.

### Methods:

Species/strain: Cynomolgus monkey

Age/weight: 2 to 4 years old; 1.9 to 3.2 kg for males and 2.0 to 2.8 kg for females.

Doses Administered: 0, 0.01, 0.03, 0.1, 0.3 and 1 mg/kg/day (Groups 1-6)

Dose volume - 10 mL/kg.

Vehicle: 0.5% methylcellulose

Sex/Number/Route: Males and females; 10, 3, 3, 5, 5, and 5/sex/Groups 1 through 6, respectively; oral gavage.

Duration of dosing/recovery: 3 weeks/ 5 weeks recovery (Groups 1-5); Group 1 and 6 were dosed for 4 weeks with 2 weeks recovery.

### Study design:

- Three males and three females in the control and 1.0 mg/kg/day groups were sacrificed after at least 4 weeks of treatment (interim sacrifice) and two males and two females in the control and 1.0 mg/kg/day groups (after treatment for 4 weeks) were sacrificed after a 2 weeks of recovery period (recovery-1 Phase).
- Remaining monkeys were sacrificed after at least 13 weeks of treatment (terminal sacrifice) or placed on at least 5 weeks of recovery (recovery-2 Phase) after 13 weeks of treatment.

| Group                      | No. of Animals |        | Dose Level <sup>c</sup><br>(mg/kg/day) | Dose Concentration <sup>c</sup><br>(mg/mL) |
|----------------------------|----------------|--------|----------------------------------------|--------------------------------------------|
|                            | Male           | Female |                                        |                                            |
| 1 (Control) <sup>a b</sup> | 10             | 10     | 0 <sup>d</sup>                         | 0 <sup>d</sup>                             |
| 2 (Low) <sup>b</sup>       | 3              | 3      | 0.01                                   | 0.001                                      |
| 3 (Low-Mid) <sup>b</sup>   | 3              | 3      | 0.03                                   | 0.003                                      |
| 4 (Mid) <sup>b</sup>       | 5              | 5      | 0.1                                    | 0.01                                       |
| 5 (Mid-High) <sup>b</sup>  | 5              | 5      | 0.3                                    | 0.03                                       |
| 6 (High) <sup>a</sup>      | 5              | 5      | 1.0                                    | 0.10                                       |

(excerpted from Applicant's report)

Endpoints: Mortality, clinical observations, body weights, food consumption, clinical pathology, ophthalmic examinations, electrocardiogram examinations, toxicokinetic, gross pathology, organ weight and microscopic evaluation.

Histopathology peer review: was performed

## Results:

### Mortality

No unscheduled deaths occurred during the study.

### *Clinical Signs*

Dose of 1 mg/kg/day resulted in severe clinical signs that resulted in cessation of dosing after 4 weeks of dosing. The clinical signs included dehydrated appearance; hunched posture; thin appearance, hypoactivity; discolored, few, no, and/or non-formed feces; and/or low or no food consumption. The observations were more pronounced in males. At 0.3 mg/kg/day, no food consumption was reported in 2 out of 5 male monkeys and dehydration and hunched appearance reported in one male monkey. An increased frequency of low or no food consumption was also reported at 0.1 mg/kg/day during the treatment period. Unremarkable clinical observations were reported during the recovery period.

### Body weights

Dose of 1 mg/kg/day resulted in 20% and 8% decreases in male and female mean body weights relative to the control group by the end of treatment period (day 1-29). The individual body weight gain data showed that some male and female monkeys lost up to 0.7 kg and 0.6 kg body weight, respectively, relative to the control monkeys (mean gain of 0.1 kg and 0 kg in male and females, respectively) during the treatment period (days 1-29). Dose of 0.3 mg/kg/day resulted in 18% and 8% decreases in male and female mean body weights relative to the control group by the end of treatment period (day 1-92). Body weight gain data showed that male and female monkeys at 0.3 mg/kg/day had decreased body weight gain of 0.2 kg and 0.1 kg relative to the control animals (mean gain of 0.4 kg and 0 kg in male and female, respectively) during the entire treatment period (Days 1-92). No significant body weight gain changes were reported at doses  $\leq$  0.1 mg/kg/day. No significant differences were reported at the end of the recovery period at all dose groups.

### Clinical Pathology

#### Hematological

Test article-related hematological changes were evident at 1 mg/kg/day (increases in RBC, Hgb, Hct, Fibrin and M/E ratio; decreases in WBC, RETIC, NEUT, MCV and PT). By the end of the recovery period the majority of the values were similar to the control values. Some of the changes (RBC, Hct and HGB) can be attributed to the decrease in food consumption, lower body weights and/or dehydration. The changes reported at doses  $\leq$  0.3 mg/kg/day

(increase in Hgb, Hct and/or Fibrin) were of lesser magnitude, not statistically significant and were not considered adverse.

#### Clinical and urine chemistry

Test article-related clinical and urine chemistry changes were evident at 1 mg/kg/day (increases in AST, SELA- $\alpha$  &  $\beta$ , magnesium, creatinine, cholesterol, CK, potassium, U albumin, iron, SAT, phospholipids; decreases in alkaline phosphatase (ALP), amylase, chloride, UIBC, SDH, total bile acid, free fatty acids (FFA), U LDH, U creatinine). By the end of the recovery period the majority of the values were similar to the controls. Some of the reported changes can be attributed to the decrease in food consumption and/or lower body weights (i.e. increase in potassium, cholesterol, magnesium, creatinine, albumin, FFA, AST and decreased chloride). The decreases in amylase and ALP activity are correlated with the microscopic findings in pancreas (zymogen granules) and bone growth. The changes reported at 0.3 mg/kg/day ( increases in creatinine, SELA- $\alpha$ , CK, AST, cholesterol and phospholipids) and at 0.1 mg/kg/day (increases in AST, SELA- $\beta$ , CK, cholesterol and phospholipids) were of lesser magnitude, but considered to be test article-related. No changes were reported at the end of the recovery period.

**Clinical and Urine Chemistry - % Change**

| Dose<br>(mg/kg/day) | Male         | Female       | Male                  | Female       | Male       | Female    |
|---------------------|--------------|--------------|-----------------------|--------------|------------|-----------|
|                     | 0.1          | 0.1          | 0.3                   | 0.3          | 1          | 1         |
| CREAT               | NS           | NS           | 40 (wk5)<br>33 (wk14) | NS           | 10 (wk5)   | NS        |
| Cholesterol         | 31<br>(wk5)  | 6 (wk5)      | 41 (wk5)              | NS           | 47 (wk5)   | NS        |
| AST                 | 46<br>(wk5)  | 272<br>(wk5) | 44 (wk5)              | 54 (wk5)     | 71 (wk5)   | NS        |
| SELA-A1             | NS           | NS           | 50 (wk5)              | 50 (wk5)     | 67 (wk5)   | NS        |
| SELA-B              | 67<br>(wk5)  | -8<br>(wk5)  | NS                    | NS           | 67 (wk5)   | NS        |
| Magnesium           | NS           | NS           | NS                    | NS           | 32 (wk5)   | NS        |
| Amylase             | NS           | NS           | NS                    | NS           | -38 (wk5)  | -25 (wk5) |
| Potassium           | NS           | NS           | NS                    | NS           | 35 (wk5)   | NS        |
| Chloride            | NS           | NS           | NS                    | NS           | -4 (wk5)   | NS        |
| Iron                | NS           | NS           | NS                    | NS           | 68 (wk5)   | NS        |
| UIBC                | NS           | NS           | NS                    | NS           | -34 (wk5)  | NS        |
| %SAT                | NS           | NS           | NS                    | NS           | 67 (wk5)   | NS        |
| FFA                 | NS           | NS           | NS                    | NS           | -56 (wk5)  | NS        |
| U CL EX             | NS           | NS           | NS                    | 46<br>(wk16) | -48 (wk3)  | NS        |
| SDH                 | NS           | NS           | NS                    | NS           | NS         | -50 (wk5) |
| Total BILE AC       | NS           | NS           | NS                    | NS           | NS         | -44 (wk5) |
| U sodium            | NS           | NS           | NS                    | NS           | NS         | 53 (wk3)  |
| U CREA              | NS           | NS           | NS                    | NS           | NS         | -54 (wk5) |
| PH                  | NS           | NS           | NS                    | NS           | -10 (wk3)  | -8 (wk3)  |
| CK                  | 881<br>(wk5) | 480<br>(wk5) | 186 (wk5)             | 13 (wk5)     | 2401 (wk5) | 48 (wk5)  |
| U albumin           | NS           | NS           | NS                    | NS           | 100 (wk5)  | NS        |
| Phospholipids       | 23<br>(wk5)  | 14<br>(wk5)  | 22 (wk5)              | 24 (wk5)     | 15 (wk5)   | 18 (wk5)  |
| ALP                 | NS           | NS           | NS                    | NS           | -48 (wk5)  | NS        |
| U LDH               | NS           | NS           | NS                    | NS           | NS         | -52 (wk5) |

Only statistically significant findings and toxicologically important findings were listed in this table  
 NS= Not statistically significant; ( ) = week; (wk5)= interim sacrifice

**Ophthalmoscopy**

There were no reported test article-related ophthalmological findings at all dose levels.

**Electrocardiographic Examination**

There were no reported test article-related ECG findings at all dose levels.

**Organ weights**

At 1 mg/kg/day, changes in organ weights were reported in the brain, lung, heart, liver, pituitary, thyroid and thymus. The increase in relative brain weight was correlated with microscopic changes in the brain. The significant decrease in the relative thymus weight at doses  $\geq 0.3$  mg/kg/day were correlated to the microscopic observation of thymic lymphocytic depletion, and as such were considered to be test article-related. The changes in lung, heart, liver, pituitary, thyroid relative organ weights at 1 mg/kg/day were not correlated with microscopic findings, therefore, toxicologic relevance is uncertain.

**Relative Organ weights - % change**

| Dose (mg/kg/day) | Male       | Female | Male      | Female    |
|------------------|------------|--------|-----------|-----------|
|                  | 0.3        | 0.3    | 1         | 1         |
| Brain            | NS         | NS     | 47        | NS        |
| Thymus           | -83 (wk13) | NS     | -46 (wk5) | NS        |
| Lung             | NS         | NS     | 16 (wk5)  | NS        |
| Heart            | NS         | NS     | -8 (wk5)  | NS        |
| Liver            | NS         | NS     | -25 (wk5) | NS        |
| Pituitary        | NS         | NS     | NS        | -26 (wk5) |
| Thyroid          | NS         | NS     | NS        | 40 (wk5)  |

*Only statistically significant and toxicologically meaningful findings were listed in this table  
 NS= Not statistically significant; (wk)= week; (wk5)= interim sacrifice; (wk7)= recovery-1 phase*

**Macroscopic observations**

Test article-related macroscopic observations were reported only at the interim sacrifice (1 mg/kg/day) and consisted of dark thyroid, dark adrenals, distended gallbladder and thickened gastric mucosa and/or dark areas on the gastric mucosa in the stomach of males. The findings in the thyroid and thymus (females) were evident at the end of the recovery period.

**Microscopic findings**

Test article-related histopathological changes were reported in multiple organs at the 1 mg/kg/day interim-sacrifice animals (3 monkeys/sex) and interim-recovery (2/sex).

These findings consisted of the following predominant effects (## indicates incidences in male/female):

- Femur and tibia bone: severe atrophy of the primary spongiosa (3/3) and moderate hypertrophy of the physis in the distal femur (2/2) and the tibia (1/1) in males and females and slight hypertrophy of the femoral articular cartilage in males (2/0).
- Gastric changes in males (marked dilated gastric glands (3/2), marked hemorrhage (2/0) and edema (1/0), slight acute inflammation (1/0), moderate hyperplasia (3/0) of fundic and pyloric columnar epithelium and moderate decreased numbers of parietal and chief cells (3/0). One male also had slight arteriopathy (1/0) characterized by medial hyaline necrosis and proliferation of the vascular wall of arterioles and small muscular arteries in the submucosa of the stomach (1/0),

- duodenum (1/0), and jejunum (1/0). The only finding in two females was slight dilatation of gastric glands.
- Ovary and corpora lutea: no maturing follicles were present (0) nor were active corpora lutea present (3). In the control group all animals (3) had developing follicles and active corpus lutea. Moderate calcareous bodies (3) and marked hyalinized corpora lutea were evident (3).
  - Adrenal cortex: moderate degeneration of the adrenal cortex in males and, to a lesser degree, females (moderate cytoplasmic eosinophilia (3/1) and moderate decreased vacuolization (3/1), slight apoptosis of zona glomerulosa (1/1), and focal slight hemorrhage /congestion (2/0).
  - Pancreas: Decreased pancreatic zymogen granules in 3 males (moderate) and 2 females (slight).
  - Lymphoid depletion of lymphoid organs (spleen (2/1), thymus (3/1) and lymph nodes (3/0) in males and females (marked). The reported lymphoid depletion may be stress-related and not direct test article related effect.
  - Brain: slight choroid plexus mononuclear infiltrates (3/3), thrombi (0/1), hemorrhage (2/1), thickening of vessel walls (1/2) and pigment deposition (1/1) in the cerebral ventricular choroid in males and females.
- The following findings were considered less pronounced effects due to lower incidence and/or severity:
- Liver: Bile duct hyperplasia (2/1).
  - Esophagus: slight muscle acute inflammation (1/0) and hyperkeratosis (2/0) in male.
  - Gallbladder: subacute inflammation (0/1), hyperplasia (1/1), eosinophil infiltrate (0/1) of the gallbladder of males and females.
  - Rectum: slight cell debris in rectal glands of 3 males.
  - Heart: subacute inflammation of the epicardial vessel and the perivascular in the heart of females (0/1).

**Recovery (interim):** The majority of the microscopic findings were recoverable after a 2-week recovery period or showed a decrease in incidence/severity. Findings were reported in the brain (slight mononuclear cell infiltrate (2/0), pigment (2/1) and accumulation of vacuolated cells(1/0)), liver (inflammation of the foci (1/0), bile duct hyperplasia (2/1), stomach (slight cell debris and mucus, glands (1/0)), thymus (slight depletion, lymphoid (0/1)) and ovary (slight hyalinized corpora lutea (2) although maturing follicles were evident) in females.

Test article-related microscopic changes were reported in the terminal sacrifice animals (3/sex/group) at doses of 0.1 and 0.3 mg/kg/day:

The following effects were pronounced and or occurred at a high incidence:

- Femur and tibia bone: marked (male) and moderate (female) atrophy of the primary spongiosa of the metaphysis of the femur (2/1), tibia (1/2) and fibula (1/0) of animals at 0.3 mg/kg/day.
- Gastric changes: minimal stomach hemorrhage (1/0), slight duodenum arteriopathy (1/0) and enteropathy (1/0) at 0.3 mg/kg/day.

- Ovary and corpora lutea: moderate increase in atretic follicles was evident (2) and lack of active corpora lutea (0) at 0.3 mg/kg/day. Maturing follicles were evident at doses  $\leq$  0.3 mg/kg/day.
- Adrenal cortex degeneration: moderately increase cytoplasmic eosinophilia (3/0), moderately decreased vacuolization at 0.3 mg/kg/day (3/2 -minimal) and one female (minimal) at 0.1 mg/kg/day.
- Pancreas: slight decrease in pancreatic zymogen granules in male (3/2).
- Lymphoid depletion in the thymus (moderate 2/0), spleen and mandibular lymph node (moderate 2/0) of males at 0.3 mg/kg/day. The reported lymphoid depletion may be stress-related and not direct test article related effect.
- Brain: minimal mononuclear cell infiltrates (3/3), minimal thickening of the vessel walls (2/2) and slight accumulation of vacuolated cells in the choroid plexus (0/1) in animals at 0.3 mg/kg/day and mononuclear infiltrates in the choroid plexus (1/0) of a male at 0.1 mg/kg/day.

The following findings were considered less pronounced effects due to lower incidence and/or severity:

- Mandibular salivary gland: slight (male) and minimal (female) decrease in cytoplasmic granules (2/1) at 0.3 mg/kg/day.
- Heart: moderate (male #s I55542 and I55543) and slight (female) coronary groove fat atrophy (2/1). Atrophy of fat in the coronary groove of the heart finding can be attributed to the severe body weight loss reported at 0.3 mg/kg/day relative to the control group (male monkey #s I55542 and I55543 had the greatest weight loss 0.4 kg and 0.7 kg, respectively; relative to other animal at 0.3 mg/kg/day group (day 1-92))

**Recovery:** All of the findings were recoverable during the 5-week recovery period.

No test article-related microscopic findings reported at doses  $\leq$  0.03 mg/kg/day.

#### **Toxicokinetics**

- Exposure to tivozanib hydrochloride increased with dose at all collection days in both sexes.
- The increases in  $C_{max}$  and AUC for both sexes were generally less than dose proportional on day 28 and 91 (0.01 to 1 mg/kg/day). On day 1, the increases in  $C_{max}$  and AUC were approximately dose proportional, with the exception of the values at 1 mg/kg/day which were greater than dose proportional. At doses of 0.03 to 1 mg/kg/day, the increase in  $C_{max}$  and AUC were approximately dose proportional on all collection days.
- Mean concentrations were higher after repeat dosing at doses  $\leq$  0.3 mg/kg/day, while concentrations were similar after repeat dosing at 1 mg/kg/day.
- $T_{max}$  values on day 1, 28 and 91 ranged from 2.6-6.7 hours, 3.3-8 hours and 2-4 hours, respectively.
- No significant (>2 fold) gender differences were reported.

- $C_{max}$  and AUC values were higher (1.1-2.9 and 1.3 to 3.8 times, respectively) on day 28 and 91 than day 1.
- Mean elimination half life ( $t_{1/2}$ ) was similar across all dose levels for both sexes on all blood collection days. Elimination half-life ( $t_{1/2}$ ) ranged from 7.7 to 9.2 hours.

**Toxicokinetics:**

|                                       | Group 1 <sup>b</sup>         |      | Group 2        |                | Group 3        |                | Group 4        |                | Group 5       |                | Group 6 <sup>c</sup> |               |
|---------------------------------------|------------------------------|------|----------------|----------------|----------------|----------------|----------------|----------------|---------------|----------------|----------------------|---------------|
| Daily Dose                            | 0 mg/kg<br>(Vehicle Control) |      | 0.01 mg/kg     |                | 0.03 mg/kg     |                | 0.1 mg/kg      |                | 0.3 mg/kg     |                | 1.0 mg/kg            |               |
| Number of Animals                     | M:10                         | F:10 | M:3            | F:3            | M:3            | F:3            | M: 5           | F: 5           | M:5           | F:5            | M:5                  | F:5           |
| <b>Toxicokinetics: (Day 1)</b>        |                              |      |                |                |                |                |                |                |               |                |                      |               |
| n                                     | NP                           | NP   | 3              | 3              | 3              | 3              | 5              | 5              | 5             | 5              | 5                    | 5             |
| $C_{max}$ (ng/mL) (SD)                | NP                           | NP   | 2.15<br>(0.35) | 2.47<br>(0.67) | 4.82<br>(1.11) | 7.07<br>(1.63) | 18.3<br>(5.4)  | 40.6<br>(9.2)  | 45.5<br>(6.9) | 68.6<br>(14.6) | 245<br>(43)          | 298<br>(111)  |
| AUC <sub>0-24hr</sub> (ng-hr/mL) (SD) | NP                           | NP   | 30.0<br>(1.3)  | 25.2<br>(1.3)  | 77.0<br>(4.2)  | 83.7<br>(17.4) | 274<br>(51)    | 436<br>(64)    | 833<br>(152)  | 929<br>(188)   | 3500<br>(701)        | 3525<br>(872) |
| <b>Toxicokinetics: (Week 4)</b>       |                              |      |                |                |                |                |                |                |               |                |                      |               |
| $C_{max}$ (ng/mL) (SD)                | NP                           | NP   | 4.72<br>(1.48) | 6.08<br>(0.92) | 8.16<br>(1.54) | 8.89<br>(1.48) | 51.7<br>(7.6)  | 70.0<br>(14.7) | 120<br>(51)   | 104<br>(16)    | 246<br>(73)          | 270<br>(55)   |
| AUC <sub>0-24hr</sub> (ng-hr/mL) (SD) | NP                           | NP   | 60.1<br>(1.0)  | 70.0<br>(6.9)  | 102 (1)        | 106<br>(17)    | 678<br>(154)   | 908<br>(145)   | 1632<br>(734) | 1430<br>(308)  | 4320<br>(1341)       | 3933<br>(453) |
| <b>Toxicokinetics: (Week 13)</b>      |                              |      |                |                |                |                |                |                |               |                |                      |               |
| $C_{max}$ (ng/mL) (SD)                | NP                           | NP   | 7.94<br>(2.34) | 7.41<br>(1.58) | 11.8<br>(1.6)  | 12.0<br>(4.3)  | 50.2<br>(10.7) | 54.7<br>(11.2) | 169<br>(38)   | 117<br>(24)    | NP                   | NP            |
| AUC <sub>0-24hr</sub> (ng-hr/mL) (SD) | NP                           | NP   | 86.9<br>(13.0) | 85.6<br>(30.4) | 146<br>(25)    | 155<br>(17)    | 619<br>(231)   | 703<br>(124)   | 2105<br>(548) | 1563<br>(247)  | NP                   | NP            |

(excerpted from Applicant's report)

**Conclusion:**

The NOAEL level after 13 weeks of dosing was 0.1 mg/kg/day (HED = 1.95 mg/day). Findings after at least 2 weeks of recovery in animals given 1.0 mg/kg/day and after at least 5 weeks of recovery in animals given 0.3 mg/kg/day indicated either full or partial recoverability.

| <b>Study title: AV-961: A 39-Week Oral Toxicity Study in Cynomolgus Monkeys With a 6-Week Recovery Period</b> |                                                              |
|---------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------|
| Study no.:                                                                                                    | 1458-006                                                     |
| Sponsor:                                                                                                      | AVEO Pharmaceuticals, Inc.<br>Cambridge, Massachusetts 02139 |
| Conducting laboratory and location:                                                                           | (b) (4)                                                      |
| Date of study initiation:                                                                                     | 30 October, 2008                                             |
| GLP compliance/QA statement:                                                                                  | Yes                                                          |
| Drug, lot #, and % purity:                                                                                    | AV-951, CDM-005 and 99.53%                                   |

*Key Findings*

- One female at 0.03 mg/kg/day was found dead on day 37 due to gavage error. An additional male was found dead at 0.1 mg/kg/day on day 173. The cause of death was not considered to be test article-related due to the lack of toxicity/morbidity in any other animal in that group (dose longer), or any other animal receiving much higher doses in the dose range-finding study.
- No test article-related effects were reported on all end points evaluated on this study at any dose level.
- NOAEL was established to be 0.1 mg/kg/day (1.3-fold the maximum recommended human dose).

*Methods:*

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 {FOTIVDA, tivozanib}

Doses/ Number/  
 Sex/Group:

| Group Number | Dose Level (mg/kg/day) | Group Assignments              |                |
|--------------|------------------------|--------------------------------|----------------|
|              |                        | Number of Animals <sup>a</sup> |                |
|              |                        | Male                           | Female         |
| 1            | Vehicle Control        | 5                              | 5              |
| 2            | 0.01                   | 5                              | 5              |
| 3            | 0.03                   | 5                              | 5 <sup>b</sup> |
| 4            | 0.1                    | 5                              | 5              |

<sup>a</sup>At the end of the 39 week administration period, 2 animals/sex/group were placed on a 6 week recovery period, however, due to unscheduled death, only one male at 0.1 mg/kg/day was placed on recovery.  
<sup>b</sup>One female (animal number 135) was found dead during Week 6 and replaced on Week 8 (animal number 10135). The replacement animal was administered the test article for 37 weeks.

*(excerpted from Applicant's report)*

Frequency of dosing      Daily for up to 273 days (39 weeks).  
 Route of administration      Oral gavage  
 Dose volume      10 mL/kg  
 Formulation/Vehicle      Vehicle, 0.5% methylcellulose  
 Sex/Species/Strain      23 male and 23 female naïve cynomolgus monkeys  
 Age      1 year and 11 months to 3 years and 11 months.  
 Weight      Body weights on Day 1 ranged from 2.42 to 3.52 kg for males and 2.16 to 3.24 g for females.  
 Satellite groups /Toxicokinetic evaluation      Blood samples were obtained from all animals at pre-dose, 0.5, 1, 2, 4, 8, 16 and 24 hours after dosing on days 1, 91 and 273 (Groups 1 – 4). The 1-hour post-dose sample collected from the control group was analyzed.

|                                |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
|--------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Endpoints evaluated            | <ul style="list-style-type: none"><li>• Mortality, clinical observations, cage side observations, ophthalmic examinations, body weight and food consumption.</li><li>• ECG was performed pre-test and 1 hour post-dose during week 39 and at the end of the recovery period. Additional ECG examination was performed pre-dose and 1 hour post-dose during week 29 for all animals at the control and 0.1 mg/kg/day groups.</li><li>• Echocardiographic examinations were performed on all animals at the control and 0.1 mg/kg/day groups during week 29.</li><li>• Clinical pathology (hematology, clinical chemistry and urine) evaluations were performed pre-test, weeks 13 and 29, from the control and 0.1 mg/kg/day animals only and prior to the terminal and recovery necropsies. Blood samples for evaluation for CPK, Troponin I and brain natriuretic peptide (BNP) were collected during week 29 from all surviving animals at the control and 0.1 mg/kg/day groups.</li><li>• Pathology evaluations (macro and microscopic) and organ weights. No histopathology peer review was performed.</li></ul> |
| Termination and necropsy:      | All surviving animals at the scheduled terminal and recovery necropsies. Histopathology evaluations were performed at all dose levels.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
| Deviation from study protocol: | None of the deviations affected the integrity or interpretability of the data.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |

*Results:*

*Analysis of dosing formulations*

- *Stability:* Samples collected from 0.01 and 0.1 mg/kg/day formulations from weeks 1 and 12 preparations were maintained in refrigerated conditions for 7 and 14 days. Results of the 7 and 14 day stability at both concentrations from week 1 preparation were outside the  $\pm 15\%$  acceptance criteria.
  - The 7 and 14 day stability results for samples at 1.0  $\mu\text{g}/\text{mL}$  were 136.6% and 144.1% of targeted concentration. The 7 and 14 day stability results for samples at 10.0  $\mu\text{g}/\text{mL}$  were 115.2% and 117.7% of targeted concentration, respectively.
  - Results of the 7 and 14 day stability from week 12 at both concentrations were within the  $\pm 15\%$  acceptance criteria:
- *Homogeneity:* Analysis of samples collected from 0.01 and 0.1 mg/kg/day week 1 formulation indicated that samples were homogenous.
- *Concentration:* Analysis of samples collected during weeks 1 through 4, 8, 12, 16, 20, 24, 28, 32, 36, 39, 40, and 44 indicated that formulations were within the targeted concentration range ( $\pm 15\%$ ). Exceptions were week 8 for 0.01 mg/kg/day (115.4% - backup samples); week 28 for 0.1 mg/kg/day (137.2%) and week 40 for 0.03 mg/kg/day (117.0%).

### *Mortality*

- One female at 0.03 mg/kg/day (animal number 135) was found dead on day 37. Microscopic findings indicated that the primary cause of death was due to a gavage error with secondary pneumonia, subsequent septicemia and abdominal involvement. Microscopic findings provided support for this assumption.
- One male (animal number 138) at 0.1 mg/kg/day was found dead on day 173. No macroscopic or microscopic findings were reported that would indicate the cause of death. There was no evidence of gavage error reported. The reported microscopic findings were minimal infiltration of mononuclear cells in the heart, kidney and liver; minimal pigmented alveolar macrophages around bronchioles in the lung and unilateral congestion of cortical sinusoids of the adrenal glands.

The death of the male at 0.1 mg/kg/day was not considered to be test article-related for the following reasons:

- Follow up studies were performed (troponin I, CK, CPK and BMP, blood pressure, ECGs and echocardiographic evaluation) on the remaining surviving animals to understand the causes of death. The findings did not provide any additional insight regarding the cause of the reported death.
- Higher doses (0.3 and 1 mg/kg/day) administered in prior 13 week study (Study # 6691-159) showed no mortalities.
- No other study animal was reported to show severe signs of toxicity, even after 273 days of dosing.

### *Clinical Signs*

There were no reported test article-related clinical observations at all dose levels.

### *Body Weights*

There were no reported test article-related body weight effects at all dose levels.

### *Ophthalmoscopy*

There were no reported test article-related ophthalmological findings at all dose levels.

### *Electrocardiographic Examination*

There were no reported test article-related ECG findings at all dose levels.

### *Echocardiographic Evaluations*

There were no reported test article-related echocardiographic findings (qualitative and quantitative abnormalities in heart size and indices of left ventricular global systolic performance) at all dose levels.

### *Clinical Pathology*

*Hematology: There were no reported test article-related hematological changes at all dose levels.*

*Coagulation:* There were no reported test article-related coagulation changes at all dose levels.

*Clinical Chemistry:* There were no reported test article-related clinical chemistry changes at all dose levels.

*Urinalysis:* There were no reported test article-related urinalysis changes at all dose levels.

#### *Macroscopic Observations*

There were no reported test article-related macroscopic findings at all dose levels.

#### *Organ weights*

There were no reported test article-related organ weight changes at all dose levels. Although decreases in heart weights in males and females were noted, they were not associated with macro-microscopic findings, ECG or echocardiographic findings.

#### *Microscopic Observations*

There were no reported test article-related microscopic findings.

#### *Toxicokinetics*

- Males and female TK parameters were not different on days 1, 91 and 273, indicating no gender effects.
- $AUC_{0-24}$ ,  $AUC_{0-t_{last}}$  and  $C_{max}$  increased in approximate proportion to dose on days 1, 91 and 273, suggesting that systemic exposure was linear.
- Mean  $AUC_{0-24}$ ,  $AUC_{0-t_{last}}$  and  $C_{max}$  were 0.823 to 1.57 times higher on days 91 and 273 than on day 1. The similarity in  $AUC_{0-24}$ ,  $AUC_{0-t_{last}}$  and  $C_{max}$  on days 91 and 273 suggests that steady-state levels were achieved by day 91, and that no further accumulation occurred beyond day 91.
- $T_{max}$  values were longer on day 1 in comparison to Days 91 and 273. Mean  $T_{max}$  on day 1 ranged from 3.60 to 4.40 hours and from 2.10 to 2.67 hours on Days 91 and 273.
- Half life ( $t_{1/2}$ ) was unaffected by dose level or duration of treatment. Elimination half-life ( $t_{1/2}$ ) ranged from 9.6 to 12.4 hours.

#### *Toxicokinetics*

|                                       | Group 1                      |     | Group 2      |              | Group 3     |             | Group 4     |             |
|---------------------------------------|------------------------------|-----|--------------|--------------|-------------|-------------|-------------|-------------|
| Daily Dose                            | 0 mg/kg<br>(Vehicle Control) |     | 0.01 mg/kg   |              | 0.03 mg/kg  |             | 0.1 mg/kg   |             |
| Number of Animals                     | M:5                          | F:5 | M:5          | F:5          | M:5         | F:5         | M: 5        | F: 5        |
| Toxicokinetics: (Day 1)               |                              |     |              |              |             |             |             |             |
| n                                     | NP                           | NP  | 5            | 5            | 5           | 5           | 5           | 5           |
| C <sub>max</sub> (ng/mL) (SD)         | NP                           | NP  | 4.19 (0.447) | 4.69 (1.02)  | 13.4 (2.80) | 10.9 (2.33) | 50.2 (13.6) | 54.4 (17.0) |
| AUC <sub>0-24hr</sub> (ng-hr/mL) (SD) | NP                           | NP  | 59.2 (11.0)  | 59.0 (8.73)  | 186 (37.5)  | 155 (26.1)  | 712 (132)   | 643 (187)   |
| Toxicokinetics: (Week 13)             |                              |     |              |              |             |             |             |             |
| C <sub>max</sub> (ng/mL) (SD)         | NP                           | NP  | 4.83 (0.856) | 4.71 (0.861) | 14.9 (3.00) | 14.0 (2.82) | 56.7 (18.8) | 44.6 (12.3) |
| AUC <sub>0-24hr</sub> (ng-hr/mL) (SD) | NP                           | NP  | 60.2 (13.9)  | 64.6 (8.48)  | 203 (31.5)  | 181 (9.5)   | 747 (187)   | 624 (197)   |
| Toxicokinetics: (Week 39)             |                              |     |              |              |             |             |             |             |
| C <sub>max</sub> (ng/mL) (SD)         | NP                           | NP  | 5.61 (0.969) | 5.25 (0.831) | 18.0 (1.32) | 18.4 (4.35) | 65.5 (5.48) | 49.1 (5.86) |
| AUC <sub>0-24hr</sub> (ng-hr/mL) (SD) | NP                           | NP  | 69.4 (11.7)  | 66.3 (9.06)  | 246 (25.7)  | 229 (42.8)  | 905 (91.9)  | 651 (184)   |

(excerpted from Applicant's report)

### Conclusion:

The test article was well tolerated at all dose levels. Although one male was found dead at 0.1 mg/kg/day on day 173, the cause of death was not considered by the Applicant to be test article-related. The NOAEL was established to be the highest dose tested 0.1 mg/kg/day (1.3-fold the maximum recommended human dose). As such, the doses in this study were insufficient to adequately establish a dose response, and this study does not provide adequate information regarding potential toxicity associated with AV-961 following repeated oral administration for 39 weeks. Accordingly, the Applicant proposed to rely on the above GLP-compliant 13-week study to inform the package insert regarding toxicities in monkeys.

## 7 Genetic Toxicology

### Overall Summary:

- KRN951 was not considered mutagenic in the *in vitro* reverse mutation assay (Ames)
- KRN951 was not considered clastogenic in the *in vitro* mammalian cell cytogenetic test. In the absence of S9 mix, extended exposure to KRN951 produced changes in chromosomal number (polyploidy and hyperdiploidy) at  $\geq 2 \mu\text{g/mL}$  (1.2-fold the RCC patient exposure at the recommended clinical dose).
- KRN951 was not considered clastogenic or aneugenic in the *in vivo* clastogenicity assay in the rodent.

### 7.1 *In Vitro Reverse Mutation Assay in Bacterial Cells (Ames)*

| <b>Study title: Bacterial Reverse Mutation Test</b> |                                        |
|-----------------------------------------------------|----------------------------------------|
| Study no.:                                          | RCK0001                                |
| Sponsor:                                            | Kirin Brewery Co. Ltd., Japan          |
| Conducting laboratory and location:                 | (b) (4)                                |
| Date of study initiation:                           | 17 February, 2003                      |
| GLP compliance:                                     | UK GLPs and OECD GLPs                  |
| QA statement:                                       | Yes                                    |
| Drug, lot #, and % purity:                          | KRN951, Lot # CDM-001 and purity 98.8% |

#### *Key Findings*

KRN951 did not show evidence of mutagenic potential under the conditions tested.

#### *Methods:*

|                                     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
|-------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Strains:                            | <i>Salmonella typhimurium</i> tester strains TA98/pKM101, TA100/pKM101, TA1535, TA1537 and <i>Escherichia coli</i> tester strain WP2 <i>uvrA</i>                                                                                                                                                                                                                                                                                                                                              |
| Concentrations in definitive study: | The doses of KRN951 used were: 5000, 1000, 200, 40 or 8 µg/plate for TA1535 and WP2 <i>uvrA</i> in the absence of S-9 mix; 1000, 200, 40, 8 or 1.6 µg/plate for TA1537 and TA100 in the absence of S-9 mix; 200, 40, 8, 1.6 or 0.32 µg/plate for TA98 in the absence of S-9 mix; and 1000, 200, 40, 8 or 1.6 µg/plate for all strains in the presence of S-9 mix.                                                                                                                             |
| Basis of concentration selection:   | The test article was initially evaluated in a dose range-finding assay in 5-strain bacterial reverse mutation assay using the plate incorporation method in the presence and absence of S9 mix. The doses used were, 5000, 1000, 200, 40 or 8 µg /plate for TA1535, TA1537, TA100 and WP2 <i>uvrA</i> in the absence of S-9 mix; and 1000, 200, 40, 8 or 1.6 µg/plate for all strains in the presence of S-9 mix. TA98 in the absence of S-9 mix was run at 200, 40, 8, 1.6 or 0.32 µg/plate. |
| Negative Control/vehicle:           | DMSO                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |

Positive control:

**3.4.1 Without S-9 mix**

| Strain          | Positive Control |
|-----------------|------------------|
| TA1535          | SA 1 µg/plate    |
| TA1537          | 9AA 50 µg/plate  |
| TA98            | 2NF 0.5 µg/plate |
| TA100           | SA 1 µg/plate    |
| WP2 <i>uvrA</i> | 4NQO 1 µg/plate  |

**3.4.2 With S-9 mix**

| Strain          | Positive Control |
|-----------------|------------------|
| TA1535          | 2AA 2 µg/plate   |
| TA1537          | 2AA 2 µg/plate   |
| TA98            | 2AA 2 µg/plate   |
| TA100           | 2AA 2 µg/plate   |
| WP2 <i>uvrA</i> | 2AA 10 µg/plate  |

*(excerpted from Applicant's report)*

Incubation & sampling time:

At 37°C for up to 3 days

*Study Validity:*

The study was valid according to regulatory standards.

*Results:*

- The negative and positive controls responded as expected.
- No increase in the number of revertant colonies was reported, with or without S9.

*Conclusion:*

KRN951 did not show evidence of mutagenic potential under the conditions tested.

**7.2 In Vitro Assays in Mammalian Cells**

| Study title: In Vitro Mammalian Cell Cytogenetic Test: Chinese Hamster Ovary Cells |                                        |
|------------------------------------------------------------------------------------|----------------------------------------|
| Study no.:                                                                         | RCK0002                                |
| Sponsor:                                                                           | Kirin Brewery Co. Ltd., Japan          |
| Conducting laboratory and location:                                                | (b) (4)                                |
| Date of study initiation:                                                          | 17 February, 2003                      |
| GLP compliance/QA statement:                                                       | UK GLPs and OECD GLPs                  |
| Drug, lot #, and % purity:                                                         | KRN951, Lot # CDM-001 and purity 98.8% |

*Key Findings*

KRN951 was not considered to be clastogenic under the conditions tested. In the absence of S9 mix, extended exposure produced changes in chromosomal number (polyploidy and

hyperdiploidy) at  $\geq 2 \mu\text{g/mL}$  (1.2-fold the RCC patient exposure at the maximum recommended clinical dose).

#### Methods

|                                                     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
|-----------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Cell line:                                          | CHO cells                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
| Exposure and concentration in the dose-range study: | Exposure was for 3 hours period and harvesting was approximately 1.5 cell cycles after initiation of exposure. The dose levels that were tested and sent for cytogenetic analysis were: <ul style="list-style-type: none"><li>• 50, 500 and 1000 <math>\mu\text{g/mL}</math> in the absence of S-9 mix (the maximum dose 1000 <math>\mu\text{g/mL}</math> was limited by osmolality).</li><li>• 10, 100, 500 and 1000 <math>\mu\text{g/mL}</math> tested in the presence of S-9 mix. (the maximum dose 1000 <math>\mu\text{g/mL}</math> was limited by toxicity).</li><li>• 10, 100 and 500 <math>\mu\text{g/mL}</math> were analyzed for concentration verification. The doses in the dose-range study were limited by the osmolality of the compound at 2000 <math>\mu\text{g/mL}</math>.</li><li>• There were no changes in pH or other osmolality of the culture medium that impacted the outcome of the study.</li></ul> |
| Exposure and Concentrations in definitive study:    | Exposure was for 3 hours in the presence of S9 and 1.5 cell cycles in the absence of S9 mix. Two harvest times were used: 1.5 cell cycles (harvest 1) post initiation of treatment and 24 hours later (harvest 2). The dose levels that were tested and sent for cytogenetic analysis were: 0.5 and 2 $\mu\text{g/mL}$ at harvest 1 and 0.5, 2, 5 and 10 $\mu\text{g/mL}$ at harvest 2 in the absence of S-9 (the maximum dose 10 $\mu\text{g/mL}$ was limited by toxicity); and doses of 10, 100 and 500 $\mu\text{g/mL}$ at harvest 1 (the maximum dose 500 $\mu\text{g/mL}$ was limited by toxicity) and 10 $\mu\text{g/mL}$ at harvest 2 in the presence of S-9 mix. Dose of 10 $\mu\text{g/mL}$ in the absence of S-9 was limited by toxicity.                                                                                                                                                                           |
| Evaluation:                                         | Following treatment, cells were harvested based on the schedule listed above. Metaphase spreads were prepared and evaluated for chromosomal damage.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| Positive control:                                   | Mitomycin C in the absence of S-9 mix; and Benzo(a)Pyrene and Cyclophosphamide in the presence of S-9 mix.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
| Formulation/Vehicle:                                | DMSO                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |

#### Results:

- Samples obtained for concentration verification analysis were within the acceptable limits of  $\pm 10\%$  error (90% to 110% of nominal concentrations) with one exception at 100 mg/mL (concentration was 89.3%).

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 {FOTIVDA, tivozanib}

- There was an increase in osmolality greater than 50 mOsm/kg at 2000 µg/mL, as compared to the control group, therefore, this dose level was not used in the definitive studies.
- The maximum level of KRN951 tested in the absence of S-9 mix was 1000 µg/mL in the dose-range study (limited by osmolality) and 10 µg/mL in the definitive study (limited by toxicity). The maximum level of KRN951 tested in the presence of S-9 mix, was 1000 µg/mL in the dose-range study and 500 µg/mL in the definitive study (both limited by toxicity).
- In the dose-range study:
  - The increases in chromosome aberrations in the absence of S-9 at 1000 µg/mL including gaps only, by totals and by frequency, 100 and 10 µg/mL by totals and by frequency, were not considered test article-related, and were attributed to the biological variability of the assay.
  - There were no other changes in chromosomal aberrations in the presence or absence of S9 at any other dose level.
- In the definitive study:
  - No test article-related changes in the number of chromosome aberrations in the presence or absence of S-9 were reported after harvest 1 and 2.
  - Due to the lack of metaphases in the absence of S9 at harvest 1 two out of the 4 doses were scored (0.5 and 2 µg/mL). Doses of 5 and 10 µg/mL were not scored.
  - Treatment with KRN951 for the longer exposure period (which provided acceptable metaphases) in the absence of S-9 mix, provided evidence of interference with the cell cycle, as demonstrated by an increase in numerical aberrations (polyploidy and hyperdiploidy) at ≥ 2 µg/mL (1.2-fold the RCC patient exposure at the maximum recommended clinical dose).

Aberration Data: Combined Summary Data  
 Experiment 2

| Dose µg/mL                       | Total cells | Aberrant cells | Mitotic Index | Gaps | Chromatid |          | Chromosome |          | Multiple aberrations | Numerical aberrations |      |       | % cells with aberrations |              | % Relative Growth by CFC |
|----------------------------------|-------------|----------------|---------------|------|-----------|----------|------------|----------|----------------------|-----------------------|------|-------|--------------------------|--------------|--------------------------|
|                                  |             |                |               |      | deletion  | exchange | deletion   | exchange |                      | Poly                  | Endo | Hyper | with gaps                | without gaps |                          |
| Absence of S-9 mix, 1st harvest  |             |                |               |      |           |          |            |          |                      |                       |      |       |                          |              |                          |
| 0.5                              | 200         | 12             | 4.80          | 8    | 2         | 1        | 2          | 0        | 0                    | 0                     | 0    | 1     | 6.0                      | 2.0          | 126                      |
| 2                                | 200         | 10             | 4.30          | 4    | 4         | 0        | 2          | 1        | 0                    | 1                     | 0    | 3     | 5.0                      | 3.0          | 50                       |
| Control                          | 400         | 19             | 4.88          | 15   | 0         | 1        | 0          | 3        | 0                    | 2                     | 0    | 2     | 4.8                      | 1.0          | 100                      |
| MMC                              | 50          | 21             | 3.10          | 5    | 11        | 12       | 3          | 4        | 0                    | 0                     | 0    | 0     | 42.0                     | 40.0         |                          |
| Absence of S-9 mix, 2nd harvest  |             |                |               |      |           |          |            |          |                      |                       |      |       |                          |              |                          |
| 0.5                              | 200         | 4              | 4.75          | 1    | 0         | 0        | 1          | 3        | 0                    | 0                     | 0    | 1     | 2.0                      | 2.0          |                          |
| 2                                | 200         | 3              | 4.80          | 0    | 1         | 0        | 0          | 2        | 0                    | 34                    | 0    | 30    | 1.5                      | 1.5          |                          |
| 5                                | 200         | 13             | 4.00          | 1    | 3         | 0        | 1          | 8        | 0                    | 70                    | 0    | 67    | 6.5                      | 6.0          |                          |
| 10                               | 200         | 4              | 3.90          | 0    | 1         | 1        | 0          | 2        | 0                    | 61                    | 0    | 35    | 2.0                      | 2.0          |                          |
| Control                          | 400         | 7              | 5.43          | 0    | 2         | 1        | 2          | 3        | 0                    | 0                     | 0    | 1     | 1.8                      | 1.8          |                          |
| Presence of S-9 mix, 1st harvest |             |                |               |      |           |          |            |          |                      |                       |      |       |                          |              |                          |
| 10                               | 200         | 8              | 4.40          | 2    | 1         | 1        | 2          | 2        | 0                    | 1                     | 2    | 3     | 4.0                      | 3.0          | 80                       |
| 100                              | 200         | 11             | 2.80          | 8    | 2         | 1        | 1          | 0        | 0                    | 1                     | 0    | 0     | 5.5                      | 2.0          | 59                       |
| 500                              | 200         | 20             | 3.65          | 17   | 1         | 2        | 0          | 0        | 0                    | 3                     | 0    | 0     | 10.0                     | 1.5          | 31                       |
| Control                          | 400         | 20             | 4.40          | 13   | 3         | 1        | 1          | 2        | 0                    | 3                     | 0    | 1     | 5.0                      | 1.8          | 100                      |
| BP                               | 200         | 48             | 3.35          | 15   | 15        | 20       | 1          | 4        | 0                    | 1                     | 0    | 1     | 24.0                     | 17.0         |                          |
| Presence of S-9 mix, 2nd harvest |             |                |               |      |           |          |            |          |                      |                       |      |       |                          |              |                          |
| 10                               | 200         | 3              | 3.10          | 1    | 1         | 0        | 0          | 1        | 0                    | 3                     | 0    | 0     | 1.5                      | 1.0          |                          |
| Control                          | 400         | 14             | 3.78          | 6    | 5         | 1        | 1          | 1        | 0                    | 5                     | 0    | 0     | 3.5                      | 2.0          |                          |

(excerpted from Applicant's report)

**Conclusion:**

KRN951 was not considered to be clastogenic under the conditions tested. In the absence of S9 mix (Phase 1 enzymatic activity), extended exposure produced changes in chromosomal

number (polyploidy and hyperdiploidy) at  $\geq 2 \mu\text{g/mL}$  (1.2-fold the RCC patient exposure at the recommended clinical dose).

### 7.3 *In Vivo Clastogenicity Assay in Rodent (Micronucleus Assay)*

| Study title: Mouse Micronucleus Test |                                                                                                                                                                                                                                                           |
|--------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Study no:                            | RCK0003                                                                                                                                                                                                                                                   |
| Sponsor:                             | Kyowas Hakko Kirin Co.,Ltd., Japan                                                                                                                                                                                                                        |
| Conducting laboratory and location:  | (b) (4)                                                                                                                                                                                                                                                   |
| Date of study initiation:            | 13 February 2003                                                                                                                                                                                                                                          |
| GLP compliance:                      | UK GLPs and OECD GLPs with the exception of the bioanalytical phase. Data anomalies were reported following an investigation performed by the Applicant. As a result the data was not considered reliable. As such data was not discussed in this review. |
| QA statement:                        | Yes                                                                                                                                                                                                                                                       |
| Drug, lot #, and % purity:           | KRN951, Lot # CDM-001 and purity 98.8%                                                                                                                                                                                                                    |

#### *Key Findings*

KRN951 was not considered to be clastogenic or aneugenic under the conditions tested.

**Methods:**

Definitive study:  
 Doses and  
 termination  
 schedule

Dosing and sacrifice was to the following schedule:

| Group | Treatment                   | Card Colour | Total number of animals |   | Sacrifice (hours after second dose) |
|-------|-----------------------------|-------------|-------------------------|---|-------------------------------------|
|       |                             |             | M                       | F |                                     |
| 1     | Vehicle                     | White       | 5                       | 5 | 24                                  |
| 2     | 80 mg/kg/day                | Green       |                         | 5 | 24                                  |
|       | 125 mg/kg/day               |             | 5                       |   |                                     |
| 3     | 125 mg/kg/day               | Yellow      |                         | 5 | 24                                  |
|       | 200 mg/kg/day               |             | 5                       |   |                                     |
| 4     | 200 mg/kg/day               | Pink        |                         | 5 | 24                                  |
|       | 320 mg/kg/day               |             | 5                       |   |                                     |
| Group | Treatment                   | Card Colour | Total number of animals |   | Sacrifice (hours after first dose)  |
| 5     | Positive control<br>4 mg/kg | Purple      | 5                       | 5 | 24                                  |

(excerpted from Applicant's report)

Route/Frequency of dosing:

Oral by gavage/Twice, 24 hours apart

Dose volume:

10 ml/kg

Formulation/Vehicle:

Methylcellulose

Species/Strain/Age:

CD1 mice

Toxicokinetic (TK):

TK study: blood was taken.

Basis of dose selection:

A dose-range study using male and female mice administered with KRN951 (2000, 1250, 320, 200 or 125 mg/kg/day) has shown that two oral doses of 320 mg/kg for males and 200 mg/kg/day for females (dose volume 10 mL/kg) were considered the maximum tolerated doses (MTD).

Negative control:

0.5% w/w Methylcellulose in water

Positive control:

Mitomycin C (MMC) administered by intraperitoneal injection at 4 mg/kg (10 mL/kg).

Clinical signs and mortality

Animals were observed for 24 hours post-dose

Necropsy

Animals were not examined internally

Rat termination, sampling time and smears preparation:

Rats were terminated 24 hours post the 2<sup>nd</sup> dose (Day 3). Positive control mice were terminated 24 hours post dose. Bone marrow samples were taken from the femurs. Bone marrow smears prepared, fixed and stained for evaluation. A minimum of 2000 polychromatic erythrocytes (PCE), including micronucleated PCE (MN-PCE), were counted for each animal. The numbers of normochromatic erythrocytes (NCE) and micronucleated NCE (MN-NCE) were also recorded for the first 1000 cells scored.

Study Validity:

The study was valid according to regulatory standards.

Results:

- Samples obtained for concentration verification analysis were within the acceptable limits of  $\pm 10\%$  error (90.1% to 100% of nominal concentrations) with exception for the 320 mg/kg dose (88.5%).
- No test article-related clinical signs reported.
- As expected, the positive control had significantly higher micronuclei and lower PCE/NCE ratio than the control group.
- There was no test article-related effects on the percentage of MN-PCE and PCE/NCE ratio in compared to the control group.

**Table 1**  
**Geometric Means for Percentage MN-PCEs with Corresponding 95 % Confidence Intervals**

| Time   | Sex     | Group                  |                        |                        |                        |                           |
|--------|---------|------------------------|------------------------|------------------------|------------------------|---------------------------|
|        |         | 1 (Control)            | 2 (125 mg/kg)          | 3 (200 mg/kg)          | 4 (320 mg/kg)          | 5 (MMC 4 mg/kg)           |
| 24 hrs | Males   | 0.06<br>(0.031, 0.104) | 0.11<br>(0.063, 0.190) | 0.09<br>(0.052, 0.161) | 0.13<br>(0.072, 0.216) | 4.75***<br>(2.845, 7.912) |
| Time   | Sex     | Group                  |                        |                        |                        |                           |
|        |         | 1 (Control)            | 2 (80 mg/kg)           | 3 (125 mg/kg)          | 4 (200 mg/kg)          | 5 (MMC 4 mg/kg)           |
| 24 hrs | Females | 0.13<br>(0.100, 0.162) | 0.08<br>(0.038, 0.155) | 0.07<br>(0.032, 0.134) | 0.03<br>(0.013, 0.068) | 2.27***<br>(1.810, 2.838) |

Key: \*\*\* =  $p < 0.001$   
 (Non-significant findings not marked)

**Table 2**  
**Mean Percentage PCE/NCE with Corresponding 95 % Confidence Intervals**

| Time   | Sex     | Group               |                       |                       |                       |                       |
|--------|---------|---------------------|-----------------------|-----------------------|-----------------------|-----------------------|
|        |         | 1 (Control)         | 2 (125 mg/kg)         | 3 (200 mg/kg)         | 4 (320 mg/kg)         | 5 (MMC 4 mg/kg)       |
| 24 hrs | Males   | 80<br>(68.2, 91.6)  | 131<br>(108.9, 153.4) | 116<br>(93.9, 138.3)  | 145<br>(123.2, 167.7) | 44***<br>(32.4, 55.8) |
| Time   | Sex     | Group               |                       |                       |                       |                       |
|        |         | 1 (Control)         | 2 (80 mg/kg)          | 3 (125 mg/kg)         | 4 (200 mg/kg)         | 5 (MMC 4 mg/kg)       |
| 24 hrs | Females | 92<br>(72.2, 112.6) | 195<br>(168.7, 222.2) | 153<br>(125.8, 179.3) | 134<br>(107.2, 160.7) | 63*<br>(43.2, 83.5)   |

Key: \* =  $p < 0.05$ ; \*\*\* =  $p < 0.001$   
 (Non-significant findings not marked)

(excerpted from Applicant's report)

*Conclusion:*

KRN951 was not considered to be clastogenic or aneugenic under the conditions tested.

## 7.4 Other Genetic Toxicity Studies

*Overall Summary:*

A structural activity relationship (SAR) for known and potential impurities present in the drug substance was performed using Derek software. Of the 39 compounds tested, 12 compounds showed structural alerts related to mutagenicity and genotoxicity (b) (4) and as such were then screened through a standard Ames assay (GLP) using *Salmonella typhimurium* TA 1535, TA 100, TA 1537, TA 98 and TA 102 strains. Eight of the compounds were found to be positive in Ames (b) (4)

|                                                                                                                                            |                                                       |
|--------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------|
| <b>Study title:</b> AV951-08275: The Analysis of Basic Structure Activity Relationships (SAR) for Tivozanib Related Structures using Derek |                                                       |
| Study no.:                                                                                                                                 | ZNA39692.001                                          |
| Sponsor:                                                                                                                                   | AVEO Pharmaceuticals<br>Cambridge, MA 02139-4134, USA |
| Conducting laboratory and location:                                                                                                        | (b) (4)                                               |
| Date of report:                                                                                                                            | 27 April 2012                                         |
| GLP compliance:                                                                                                                            | No                                                    |

**Objective:** To identify any potential genotoxic impurities that could be present in the tivozanib hydrochloride drug substance. The structures of all starting materials, reagents, solvents, isolated and *in-situ* intermediates, and known and potential impurities, were assessed based on their reported presence and level in the drug substance.

**Method:**

Thirty-eight compounds, in addition to tivozanib hydrochloride, were evaluated using the Derek structure activity software. These compounds included starting materials, reagents, solvents, isolated and *in-situ* intermediates and known and potential impurities.

**Results and conclusion:**

Of the 39 compounds tested, 12 compounds showed structural alerts related to mutagenicity and genotoxicity (b) (4)

*In Vitro Reverse Mutation Assay in Bacterial Cells (Ames)*

**Study numbers 790081, 790102, 790118, 790123, 790139, 790097, 790144, 790165 and 790338 (combined review).**

*Conclusion:*

- (b) (4) was not considered to have mutagenic potential.
- (b) (4) was considered to have mutagenic potential.

## 8 Reproductive and Developmental Toxicology

### *Overall Summary:*

In the dose range (at 0.03, 0.1, 0.3 or 1 mg/kg/day) and definitive fertility and reproduction toxicity studies (at 0.01, 0.03 or 0.1 mg/kg/day), KRN951 was administered orally by gavage to male rats for up to 28 days before mating, during mating (1 to 14 days) and up to termination (approximately 49 total doses) and to female rats for up to 21 days prior to mating, through mating and on Gestation Days (GD) 0 to 7.

At 1 mg/kg/day, mortalities were evident in both sexes. Clinical observations and decreases in body weights were reported in both sexes at doses  $\geq 0.3$  mg/kg/day. A decrease in food consumption was reported in males at doses  $\geq 0.3$  mg/kg/day and in females at doses  $\geq 0.1$  mg/kg/day. At 1 mg/kg/day, mating was affected as evident by the increase in number of days in cohabitation, and decrease in number of male and female rats that mated. Doses  $\geq 0.3$  mg/kg/day affected the fertility index (number of pregnancies per number of rats mated) as evident by the decrease in number of rats pregnant per rats in cohabitation.

Relative epididymal weights were increased at doses  $\geq 0.03$  mg/kg/day by up to 24%, and relative testis weights were increased by 19% at doses  $\geq 0.3$  mg/kg/day. There were no effects on gonadal function or pregnancy at doses  $\leq 0.03$  mg/kg/day, while embryo lethality was evident at doses  $\geq 0.1$  mg/kg/day. The NOAEL for mating and fertility was established at 0.1 mg/kg/day (0.64-fold the human maximum recommended clinical dose) and the NOAEL for male systemic toxicity was established to be 0.03 mg/kg/day (0.19-fold the recommended human clinical dose).

In the embryo-fetal developmental study in rats, KRN951 at doses of 0.003, 0.01, 0.03 or 0.09 mg/kg/day was administered orally by gavage throughout organogenesis. Maternal toxicity (decreases in body weight gain) was evident at doses  $\geq 0.03$  mg/kg/day. Increases in the mean number of dams with resorptions and in the percent of resorbed conceptuses per litter were evident at doses  $\geq 0.03$  mg/kg/day. Significant increases in fetal external malformations (body

edema, short tail and kinked tail) were evident at 0.09 mg/kg/day (0.58-fold the maximum human recommended clinical dose), and skeletal developmental delays were reported at doses  $\geq$  0.03 mg/kg/day (0.19-fold the maximum human recommended clinical dose). A NOAEL for maternal and embryo-fetal toxicity was established to be 0.01 mg/kg/day (0.06-fold the maximum human recommended clinical dose).

In the rabbit embryo-fetal developmental study, pregnant rabbits were dosed (0.01, 0.1 or 1 mg/kg/day) throughout organogenesis. There was no reported maternal toxicity at any dose. Embryo-fetal toxicity was evident at 1 mg/kg/day (VSD, constricted pulmonary artery vessels and distended aorta). The NOAEL for maternal toxicity was established to be greater than 1 mg/kg/day (13-fold the maximum recommended human clinical dose), while the NOAEL for embryo-fetal toxicity was established to be 0.1 mg/kg/day (1.3-fold the maximum recommended human clinical dose).

### 8.1 Fertility and general reproduction toxicity studies

|                                                                                                                     |                 |
|---------------------------------------------------------------------------------------------------------------------|-----------------|
| <b>Study title:</b><br>Oral (Gavage) dose-range fertility and general reproduction toxicity study of KRN951 in rats |                 |
| Study no.:                                                                                                          | 311-007P        |
| Study report location:                                                                                              | eCTD 4.2.3.5.1  |
| Conducting laboratory and location:                                                                                 | (b) (4)         |
| Date of study initiation:                                                                                           | 09 May 2003     |
| GLP compliance:                                                                                                     | Yes             |
| QA Statement                                                                                                        | Yes             |
| Drug, lot #:                                                                                                        | KRN951, CDM-001 |

#### Key findings:

- At 1 mg/kg/day, test-article administration resulted in mortalities in both sexes.
- Doses  $\geq$  0.3 mg/kg/day resulted in clinical observations, decreases in body weights and food consumption.
- At 1 mg/kg/day, test-article administration resulted in effects on mating as evident by the increase in number of days in cohabitation and decrease in number of male and female rats that mated.
- Doses  $\geq$  0.3 mg/kg/day resulted in effects on fertility as evident by the decrease in number of pregnancies per number of rats mated and number of rats pregnant per rats in cohabitation.
- Doses  $\geq$  0.03 mg/kg/day resulted in an increase in epididymis weight (up to 24%) and at doses  $\geq$  0.3 mg/kg/day testis weight increased by up to 19%, respectively.
- Doses  $\geq$  0.1 mg/kg/day, resulted in an increase in nonviable embryos per litter and number of dams with nonviable embryos (embryo lethality).

### Objectives:

To provide information for the selection of dosages to be used in the fertility and general reproduction toxicity study of KRN951 administered orally via gavage to CrI:CD®(SD)IGS BR VAF/Plus® male and female rats.

### Methods:

- Species and sex: male and female rats
- Strain: CrI:CD® (SD)IGS BR VAF/Plus®
- Supplier: (b) (4)

### Study design:

|         | Dose (mg/kg/day) | Dose Volume (ml/kg) | Number of Rats/sex |
|---------|------------------|---------------------|--------------------|
| Group 1 | Vehicle          | 10                  | 8                  |
| Group 2 | 0.03             | 10                  | 8                  |
| Group 3 | 0.1              | 10                  | 8                  |
| Group 4 | 0.3              | 10                  | 8                  |
| Group 5 | 1.0              | 10                  | 8                  |

- *Vehicle*: Aqueous 0.5% w/v Methylcellulose.
- Suspension of Test-Article, KRN951 was prepared weekly.
- Analysis: Concentration and homogeneity were evaluated on study. Stability data for the prepared formulation bracketing the range of concentrations used in study were provided by the Applicant.
- Route: Oral gavage.
- Dosing:
  - Males - daily for 21 days prior to cohabitation and through the day before sacrifice. Maximum doses administered: 42 doses.
  - Females - 21 days before cohabitation and through Gestation Day (GD) 7. Maximum doses administered: 42 doses.
- Cohabitation period:
  - Treated male were cohabited with treated females from the same dose group for 14 days. Female rats not mated within the first 14 days of cohabitation were assigned alternate male rats (same dosage group) that had mated and remained in cohabitation for a maximum of five additional days.
- Female rats with spermatozoa observed in a smear of the vaginal contents and/or a copulatory plug *in situ* were considered to be GD 0.
- Cesarean section (C-section): GD 13.
- In-life endpoints:
  - Mortalities and clinical observations.
  - Daily post-dose observations (1 hour and 4 hours).
  - Body weight – weekly during the pre-dose period and daily during the dosing period and post-dosing period and at necropsy.

- Food consumption – weekly during the dosing period (males) except during the cohabitation period. For females weekly to cohabitation and on GD 0, 7, 8, and 13.
- Estrous cycling was evaluated (vaginal cytology) during the cohabitation period until spermatozoa were observed in a smear of the vaginal contents and/or a copulatory plug was observed *in situ*.
- Males were sacrificed and necropsied after cohabitation following at least 42 days of dosing. Male reproductive organs were weighed and retained for possible histological evaluation.
- Females were sacrificed on GD13 followed by C-section and gross necropsy. Number of corpora lutea was recorded. Uterus was examined for implantation sites and viable/nonviable embryos.

### Results:

Analysis of test formulations:

Concentration ( $\pm 15\%$ ) of the test-article in the formulations were within the acceptable criteria with the exception of deviations in group 4 and 5 (0.03 mg/mL and 1.0 mg/mL) for formulations prepared on 5/14/2003 (+39.5% and +24.2%, respectively) and group 3 (0.003 mg/mL) and 5 (0.1 mg/mL) for formulations prepared on 6/30/2003 (-17.6% and -17.1%, respectively). The formulation was stable for up to 15 days after preparation at (4°C) and for at least one day at room temperature.

Homogeneity ( $\leq 5\%$  RSD) of the test-article in the formulations was within the acceptable criteria with the exception of deviations on 5/14/2003 in group 4 and 5 (+10.3% and +15.2%, respectively).

*Mortality and clinical observations (male and female):*

Found dead and moribund sacrificed were reported only at 1 mg/kg/day in males and females:

### Mortalities:

| Dose<br>(mg/kg/day) | Found dead     |        | Moribund sacrificed |                   |
|---------------------|----------------|--------|---------------------|-------------------|
|                     | Male           | Female | Male                | Female            |
| Vehicle             | 0              | 0      | 0                   | 0                 |
| 1.0                 | 2 (SD 17 & 31) | 0      | 2 (SD 37 & 41)      | 3 (SD 6, 33 & 41) |

*SD=study day*

Clinical observations were reported prior to death or sacrifice, and included dehydration, chromorhinorrhea, chromodacryorrhea, cold to touch, lacrimation, decreased motor activity, pale extremities, miosis, emaciation, hyperpnea, ungroomed coat, urine-stained abdominal fur, mucoid feces, soft feces, liquid feces, scant feces, no feces in the cage pan, hunched posture, emaciation, impaired righting reflex and/or labored breathing.

Surviving male and female rats to scheduled termination at 0.3 and 1 mg/kg/day, exhibited adverse clinical signs that included: ungroomed coat, dehydration, chromorhinorrhea, soft or liquid feces, chromodacryorrhea and lacrimation. Other clinical signs reported only at 1 mg/kg/day were scant feces, urine-stained abdominal fur, decreased motor activity, cold to touch, pale extremities, hunched posture, emaciation, impaired righting reflex, brown or red per-oral substance, ptosis, hyperpnea, labored breathing, mucoid feces and/or no feces in cage pan.

*Body weight (male and female):*

- At 1 mg/kg/day, a decrease ranging between 6% to 43%, in male mean body weight was reported during SD 11 to 42. The severity of the effect was more pronounced at latter study days.
- Decreases in male body weight gains were reported at 0.03, 0.1, 0.3 and 1 mg/kg/day by up to 20%, 36%, 50% and 252%, respectively.
- At 1 mg/kg/day, a decrease in female mean body weight (up to 8%) was reported during study days 18 to 21 (pre-cohabitation period) and a decrease in body weight gain (up to 101%) during the entire pre-cohabitation period.

*Food consumption (male and female):*

- Male mean absolute and relative feed consumption values were reduced at 0.1, 0.3 and 1.0 mg/kg/day by up to 6%, 8% and 39% during the entire study period.
- Female mean absolute and relative feed consumption values were reduced at 0.3 and 1.0 mg/kg/day during the entire pre-cohabitation period (study day 1 to 21) by 10% and 24%, respectively.

*Mating and fertility:*

*Males*

The number of days in cohabitation (number of days required to inseminate) was increased for the male rats at 1.0 mg/kg/day, in comparison with the control group (3.7 days versus 2.7 days, respectively). The number of male rats that mated (83.3%) was also reduced at 1.0 mg/kg/day, compared to the control group (100%). The fertility index (number of pregnancies per number of rats mated) and the number of rats pregnant per rats in cohabitation were 0.0% at 0.3 and 1.0 mg/kg/day.

*Females*

The number of days in cohabitation was increased for the female rats at 1.0 mg/kg/day, in comparison with the control group (5.1 days versus 2.7 days, respectively). The number of female rats that mated was also reduced at 1.0 mg/kg/day, in comparison with the control group (71.4% versus 100%, respectively). The fertility index (number of pregnancies per number of rats mated) and the number of rats pregnant per rats in cohabitation were 0.0% (none mated) at 0.3 and 1.0 mg/kg/day dosage groups.

All mating and fertility parameters for male and female rats were unaffected at  $\leq 0.1$  mg/kg/day.

*Male necropsy and organ weights:*

Several gross lesions were reported at necropsy. At 0.3 mg/kg/day, one male rat had a mass on the right cauda epididymis.

At 1 mg/kg/day, two male rats had adrenals that appeared large and red (bilateral), kidneys that appeared pale (bilateral), and air-filled stomach; one additional rat had a liver mass.

Relative epididymis weights were increased 13%, 18%, 24% and 19% at 0.03, 0.1, 0.3 and 1 mg/kg/day, respectively. Relative testis weights were increased by 10% and 19% at 0.3 and 1 mg/kg/day.

*Female Cesarean section and necropsy:*

No gross lesions were reported at necropsy of rats survived to C-section.

None of the surviving female rats at either the 0.3 or 1.0 mg/kg/day were found pregnant.

At 0.1 mg/kg/day, an increases in the number of dams with any nonviable embryos (62.5% vs 28.6% at the control, respectively) and percent nonviable embryos per litter (5.8% vs. 2.8% at the control, respectively) were reported.

**Conclusion:**

- KRN951 (0.03, 0.1, 0.3 or 1 mg/kg/day) was administered orally by gavage to male rats for 21 days before mating, during mating (1 to 14 days) and up to termination and to female rats for 21 days prior to mating, through mating and on GD 0 to 7. Doses  $\geq 0.3$  mg/kg/day resulted in mortalities, clinical observations, decreases in body weights, decrease in food consumption, reduced mating and fertility. Relative epididymis weights were increased at doses  $\geq 0.03$  mg/kg/day and relative testis weights were increased at 0.3 mg/kg/day. An increase in nonviable embryos per litter and number of dams with nonviable embryos was evident at doses  $\geq 0.1$  mg/kg/day.

**Study title:**

Oral (Gavage) fertility and general reproduction toxicity study of KRN951 in rats

|                                     |                 |
|-------------------------------------|-----------------|
| Study no.:                          | 311-007         |
| Study report location:              | eCTD 4.2.3.5.1  |
| Conducting laboratory and location: | (b) (4)         |
| Date of study initiation:           | 11 August 2003  |
| GLP compliance:                     | Yes             |
| QA Statement                        | Yes             |
| Drug, lot #:                        | KRN951, CDM-001 |

**Key findings:**

In males, there were no reported test article-related clinical observations, body weight and food consumption effects at all dose levels. Mating, reproductive organ weights, sperm count and motility were not affected at all dose levels.

In females, there were no reported test article-related clinical observations and body weight effects at all dose levels. However, relative food consumption was statistically significantly decreased during the gestation period (GD 8-13) at 0.1 mg/kg/day. Estrous cycle and mating incidence, days needed for mating or pregnancy incidence were not affected by the test article treatment. The number of litters with nonviable embryos was not affected by treatment at all dose groups. Placentae appeared normal at all dose groups.

**Objectives:**

To determine the potential effects of KRN951, when administered orally to male and female rats, on mating, fertility and gonadal function and on pregnancy and early embryonic period.

**Methods:**

- Species and sex: Male and female rats
- Strain: CrI:CD<sup>®</sup> (SD)IGS BR VAF/Plus<sup>®</sup>
- Supplier: (b) (4)
- Age at arrival: Males 63 days; females 63 days
- Weight at study assignment: Males 314-365 g; females 219-286 g
- After the acclimation period and estrous cycle evaluation, female rats were selected for study on the basis of physical appearance, body weights recorded during the predosage period and evidence of normal estrous cycling.

**Study design:**

|         | Dose (mg/kg/day) | Dose Volume (ml/kg) | Number of Rats/sex |
|---------|------------------|---------------------|--------------------|
| Group 1 | Vehicle          | 10                  | 25                 |

|                |      |    |    |
|----------------|------|----|----|
| <b>Group 2</b> | 0.01 | 10 | 25 |
| <b>Group 3</b> | 0.03 | 10 | 25 |
| <b>Group 4</b> | 0.1  | 10 | 25 |

- Vehicle: Aqueous 0.5% w/v Methylcellulose.
- Suspension of Test Article, KRN951 was prepared weekly.
- Analysis: Concentration and homogeneity were evaluated on study. Stability data for the prepared formulation bracketing the range of concentrations used in study were provided by the sponsor to the contact laboratory.
- Route: Oral gavage.
- Dosing:
  - Males - Daily for 28 days before cohabitation and through a 14-day cohabitation period, until the day before sacrifice (up to 49 days). Maximum doses administered: 47 doses.
  - Females - 15 days before cohabitation through Gestation Day (GD) 7. Maximum doses administered: 47 doses.
- Cohabitation period: Treated male were cohabited with treated females from the same dose group for 14 days. Female rats not mated within the first 14 days of cohabitation were assigned alternate male rats (same dosage group) that had mated, and the pair remained in cohabitation for a maximum of five additional days.
- Female rats with spermatozoa observed in a smear of the vaginal contents and/or a copulatory plug *in situ* were considered to be at GD 0.
- Cesarean section (C-section): GD 13.
- In-life endpoints:
  - Mortalities and clinical observations.
  - Daily post-dose observations (1 hour and 4 hours).
  - Body weight – weekly during the pre-dose period and daily during the dosing period and post-dosing period (females) and at necropsy.
  - Food consumption – weekly during the dosing period (males) except during the cohabitation period. For females weekly to cohabitation and on GD 0, 7, 8, 10 and 13.
  - Estrous cycling was evaluated (vaginal cytology) for 14 days pre-dose, for 14 days during dosing and then until spermatozoa was observed in a smear of the vaginal contents and/or a copulatory plug was observed *in situ* during the cohabitation period.
- Males were sacrificed and necropsied after cohabitation. Male reproductive organs were weighed and retained for possible histological evaluation. Sperm concentration and motility were evaluated. Motility was evaluated by the Hamilton Thorne IVOS using samples collected from the left vas deferens. A homogenate was prepared from the left cauda epididymis for evaluation by the Hamilton Thorne IVOS to determine sperm concentration (sperm per gram of tissue weight).

- Females were sacrificed on GD 13 followed by caesarean section and gross necropsy. Number of corpora lutea was recorded. Uterus was examined for implantation sites and viable and nonviable embryos.

**Results:**

Analysis of test formulations:

Concentration ( $\pm 15\%$ ) and homogeneity ( $\leq 5\%$  RSD) of the test article in the formulations were within the acceptable criteria with the exception of deviations in group 2 (0.001 mg/mL) for formulations prepared on 10/6/2003. The formulation was stable for up to 15 days after preparation at 4°C and for at least one day at room temperature.

*Mortality and clinical observations (male and female):*

All rats survived to scheduled termination. There were no test article-related clinical observations.

*Body weight and food consumption (male and female):*

There were no reported test article effects on body weights at all dose levels in both sexes. Male food consumption was not affected by the test article treatment at all dose levels, while female relative food consumption was decrease by 6% during GD 8 to 13 at 0.1 mg/kg/day.

*Male mating, necropsy, organ weights, sperm count and motility:*

There were no test article-related effects reported on mating incidence, days taken for mating or pregnancy incidence. There were no test article-related changes reported during necropsy and no effect on reproductive organ weights. There were no test article-related effects on the number and percent motile sperm, number of non-motile sperm and total sperm count from the vas deferens and caudal epididymal (sperm count and density).

*Female estrous cycle and mating, cesarean section and necropsy:*

There were no test article-related necropsy observations. There were no test article-related effects on the estrous cycle, mating incidence, days needed for mating or pregnancy incidence. There were no test article-related effects on numbers of corpora lutea, implantations, litter size, viability of embryos at all dose levels. Placentae appeared normal at all dose groups.

**Conclusion:**

KRN951 (0.01, 0.03 or 0.1 mg/kg/day) was administered orally by gavage to male rats for 28 days before mating, during mating (1 to 14 days) and up to termination (approximately 49 total doses) and to female rats for 14 days prior to mating, through mating and on GD 0 to 7. There were no effects on mating, fertility, gonadal function, or embryo viability at all dose levels.

## **8.2 Embryo-fetal developmental toxicity studies**

|                                                                                     |                 |
|-------------------------------------------------------------------------------------|-----------------|
| <b>Study title:</b><br>Oral (gavage) developmental toxicity study of KRN951 in rats |                 |
| Study no.:                                                                          | 311-005         |
| Study report location:                                                              | eCTD 4.2.3.5.2  |
| Conducting laboratory and location:                                                 | (b) (4)         |
| Date of study initiation:                                                           | 11 August 2003  |
| GLP compliance:                                                                     | Yes             |
| QA Statement                                                                        | Yes             |
| Drug, lot #:                                                                        | KRN951, CDM-001 |

**Key Findings:**

Maternal toxicity (decreases in body weight gain) was evident at doses  $\geq 0.03$  mg/kg/day. An increase in mean number of dams with resorptions and in percent of resorbed conceptuses per litter was evident at doses  $\geq 0.03$  mg/kg/day. Significant increases in external malformations (body edema, short tail and kinked tail) were evident at 0.09 mg/kg/day, and skeletal developmental delays were reported at doses  $\geq 0.03$  mg/kg/day.

**Objectives:**

The purpose of the study was to evaluate the adverse effects of KRN951 on CrI:CD® (SD)IGS BR VAF/Plus® presumed pregnant female rats and development of the embryo and fetus consequent to exposure of the dam from implantation to closure of the hard palate. This study was designed to evaluate ICH Harmonised Tripartite Guideline stage C and D of the reproductive process.

**Methods:**

- Species: Male and Female Rats (males used only for breeding)
- Strain: CrI:CD® (SD)IGS BR VAF/Plus
- Supplier: (b) (4)
- Age at arrival: 62 days
- Weight at study assignment: 218-246 g

**Study design:**

|                | Dose<br>(mg/kg/day) | Dose Volume<br>(ml/kg) | Number of<br>Rats |
|----------------|---------------------|------------------------|-------------------|
| <b>Group 1</b> | Vehicle             | 10                     | 25                |
| <b>Group 2</b> | 0.003               | 10                     | 25                |
| <b>Group 3</b> | 0.01                | 10                     | 25                |
| <b>Group 4</b> | 0.03                | 10                     | 25                |
| <b>Group 5</b> | 0.09                | 10                     | 25                |

- Vehicle: Aqueous 0.5% w/v Methylcellulose.
- Suspension of KRN951 was prepared weekly.
- Analysis: Concentration and homogeneity were evaluated on study. Stability data for the prepared formulation bracketing the range of concentrations used in study were provided by the sponsor to the contract laboratory.
- Females with evidence of a sperm positive vaginal smear were randomized and assigned to study groups.
- Dosing:  
Females: Daily from Gestation Day (GD) 7 to 17 (Day 0= Day 1 of gestation). Males: were not dosed.
- Route: Oral gavage.
- Cesarean section (C-section): GD 21.
- In-life endpoints:
  - Mortalities and clinical observations.
  - Daily post-dose observations (1 hour and 4 hours).
  - Body weight - Daily.
  - Food consumption - GD 1, 7, 10, 12, 15, 18 and 21.
- Litter endpoints: Uterus weight, number of corpora lutea, number of live fetuses, number of dead fetuses and resorptions.
- Fetal end points: Sex, fetal weights, external, visceral and skeletal examination.

#### **Results:**

Analysis of test formulations:

Concentration and homogeneity of the test article in the formulations were within the acceptable criteria with the exception of deviations in group 2 (0.003 mg/kg/day) for formulations prepared on 4 days (-15.8% to 70.4% for concentration and 33.4% on one day for homogeneity). The formulation was stable for up to 15 days after preparation at (4°C) and for at least one day at room temperature.

*Maternal data:*

*Mortality and clinical observations:*

All rats survived to scheduled termination. There were no treatment-related clinical observations.

*Body weight and Food consumption:*

- A decrease in body weight gain was reported at 0.09 mg/kg/day group in comparison to the control group, during GD 15-18 (17%) and during the entire dosing period (11% at GD 7-17). Mean body weights were not affected by the treatment at all dose levels.
- Body weight gain at 0.03 mg/kg/day, was decreased by 8% during the entire dosing period (GD 7-17).
- There was no drug-related effect on mean food consumption at all dose levels.

*Litter data:*

- Mean number of dams with resorptions at 0.09 mg/kg/day, was reported to be 64% higher than the control group. The reported increases in total resorptions were attributed to the increases in mean number of early resorptions (not statistically significant) at 0.09 mg/kg/day.
- The percent of resorbed conceptuses per litter was higher at 0.03 mg/kg/day (5.3%) and 0.09 mg/kg/day (7.4%), relative to control (3.5%).
- There were no effects on fetal weights.

*Fetal Data:*

- 100%, 58%, 25% and 48% of the litters at 0.09, 0.03, 0.01, and 0.003 mg/kg/day, respectively, were reported to have fetuses with anatomical abnormalities (malformations and/or variations) in comparison to 8% of the fetuses at the control group.
- The percent of fetuses with any anatomical abnormalities per litter was higher at 0.09 mg/kg/day (70%) in comparison to the control group (0.5%).
- The percent of litters with fetuses with any malformation was higher at 0.09 mg/kg/day (96%) in comparison to the control group (0%). The percent of fetuses with malformation per litter at 0.09 mg/kg/day was 59%, in comparison to 0% at the control group.
- The percent of fetuses with any variations per litter was higher at 0.09 mg/kg/day (11.7%) and 0.03 mg/kg/day (4.2%) in comparison to the control group (0.5%).
- Significant increases in external malformations were reported at 0.09 mg/kg/day and included, body edema, short tail and kinked tail.
- Significant increases in skeletal variations were reported at 0.09 mg/kg/day. The variations were reported to be in the thoracic vertebra (centrum unilateral ossification and centrum bifid), lumbar vertebrae (bifid centrum), caudal vertebrae (centrum unilateral ossification), sternal centra (incompletely ossified). At 0.03 mg/kg/day, the only toxicologically important variation report was in the thoracic vertebra (centrum bifid).
- The mean number of ossification sites per fetus per litter (caudal vertebrae, forelimb phalanges, metatarsals and hindlimb phalanges) were decreased at 0.09 mg/kg/day in comparison to the control group. Additionally, a decrease in the number of caudal vertebrae ossification sites per fetus per litter was reported at 0.03 mg/kg/day in comparison to the control group. The decrease in number of ossifications may be an indication of developmental delay.

**Conclusion:**

In the embryo-fetal developmental study, KRN951 at doses of 0.003, 0.01, 0.03 or 0.09 mg/kg/day was administered orally by gavage to pregnant rats throughout organogenesis. Maternal toxicity was evident at doses  $\geq$  0.03 mg/kg/day. Increases in mean number of dams with resorptions and in percent of resorbed conceptuses per litter were evident at doses  $\geq$  0.03. At 0.09 mg/kg/day, external malformations,

and fetal developmental delay (skeletal variations) were apparent at doses  $\geq 0.03$  mg/kg/day. NOAEL was established at 0.01 mg/kg/day.

|                                    |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
|------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Study #:</b><br><b>311-006p</b> | <p><b>Title:</b> Oral (Stomach Tube) Dosage-Range Developmental Toxicity Study of KRN951 in Rabbits</p> <p><b>Conducting Laboratory:</b><br/> (b) (4)</p> <p><b>Date of study initiation:</b> 09 May, 2003<br/><b>GLP compliance:</b> Yes<br/><b>QA statement:</b> Yes</p> <p><b>Objective and Methods:</b><br/>The objective of the dose range study was to establish doses for the pivotal embryo-fetal developmental study in rabbits.</p> <p>Timed-mated pregnant New Zealand White rabbits (n=24) were randomly assigned to four dose groups (0, 0.01, 0.1 and 1.0 mg/kg/day). Test article and vehicle were administered orally once daily on Gestation Days (GD) 6 through 18. The dosage volume was 10 ml/kg. Viability, clinical observations, body weights, food consumption, corpora lutea, implantations, resorptions, live and dead fetuses, fetal weight, fetal sex and external (all dosage groups), visceral (control and 1 mg/kg/day) and skeletal (control and 1 mg/kg/day) findings were recorded.</p> <p><b>Results:</b></p> <ul style="list-style-type: none"><li>• At 1 mg/kg/day, mean body weights and food consumption values were decreased (GD 12 to 29).</li><li>• At doses <math>\geq 0.1</math> mg/kg/day, mean numbers of early resorptions and the percentage of dead or resorbed conceptuses per litter were increased.</li><li>• At doses <math>\geq 0.1</math> mg/kg/day, fetal body weights were reduced. Reductions in fetal weights were greatest for male fetuses.</li><li>• At 1 mg/kg/day, the following fetal external findings were reported: one fetus with meningocele, open eyelids of the right eye. One fetus had an inwardly flexed left forepaw.</li><li>• At 1 mg/kg/day, the following fetal visceral findings were reported: one fetus had corneal opacity of the right eye. Interventricular septal defect (VSD) was reported in two fetus from two different litters. One of the two</li></ul> |
|------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

|  |                                                                                                                                                                                                                                                                                                                                   |
|--|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|  | <p>fetuses with the VSD also had distended aorta and constricted pulmonary artery.</p> <ul style="list-style-type: none"> <li>At 1 mg/kg/day, external and skeletal variations were reported.</li> </ul> <p><b>Conclusion</b><br/>                 Doses of 0.01, 0.1 and 1 mg/kg/day were recommended for the pivotal study.</p> |
|--|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

|                                                                                                                                    |                 |
|------------------------------------------------------------------------------------------------------------------------------------|-----------------|
| <b>Study title:</b><br>Oral (stomach tube) Developmental Toxicity Study of KRN951 in Rabbits, Including a Toxicokinetic Evaluation |                 |
| Study no.:                                                                                                                         | 311-006         |
| Study report location:                                                                                                             | eCTD 4.2.3.5.2  |
| Conducting laboratory and location:                                                                                                | (b) (4)         |
| Date of study initiation:                                                                                                          | 16 January 2004 |
| GLP compliance:                                                                                                                    | Yes             |
| QA Statement                                                                                                                       | Yes             |
| Drug, lot #:                                                                                                                       | KRN951, CDM-001 |

**Objectives:**

The purpose of this study was to detect adverse effects of KRN951 on New Zealand White [Hra:(NZW)SPF] presumed pregnant female rabbits and development of the embryo and fetus consequent to exposure of the doe from implantation to closure of the hard palate. This study was designed to evaluate ICH Harmonised Tripartite Guideline stages C and D of the reproductive process in a non rodent species.

**Methods:**

- Species: Rabbit (Timed-mated female)
- Strain: Hra:(NZW)SPF
- Supplier: (b) (4)
- Age at arrival: 5 months
- Weight at study assignment: 2.5-4.2 kg

**Study design:**

|                | Dose (mg/kg/day) | Dose Volume (ml/kg) | Number of Main Study Rabbits | Number of TK Rabbits |
|----------------|------------------|---------------------|------------------------------|----------------------|
| <b>Group 1</b> | Vehicle          | 10                  | 20                           | 0                    |
| <b>Group 2</b> | 0.01             | 10                  | 20                           | 3                    |
| <b>Group 3</b> | 0.1              | 10                  | 20                           | 3                    |
| <b>Group 4</b> | 1.0              | 10                  | 20                           | 3                    |

- Vehicle: Aqueous 0.5% w/v Methylcellulose.
- Suspension of Test Article, KRN951 was prepared weekly.
- Analysis: Concentration and homogeneity were evaluated on study. Stability data for the prepared formulation bracketing the range of concentrations used in study were provided by the sponsor to the contract laboratory.
- Timed-mated females were randomized and assigned to study groups.
- Dosing: Daily from Gestation Day (GD) 6 to 18. The day of mating was considered to be GD 0.
- Route: Oral gavage.
- Cesarean section (C-section) main study rabbits: GD 29.
- In-life end points:
  - Mortalities and clinical observations.
  - Daily post-dose observations (1 hour).
  - Body weight - Daily.
  - Food consumption - Daily.
- Litter endpoints: Uterus weight, number of corpora lutea, number of live fetuses, number of dead fetuses, resorptions and fetal weight.
- Fetal endpoints: Sex, external, visceral and skeletal examination.
- Toxicokinetic (TK): Blood was collected on GD 6 and 18 for TK analysis at 30 minutes, 2 hours, 4 hours, 8 hours and 24 hours post-dose.

**Results:**

Analysis of test formulations:

Concentration (acceptable range  $\pm 15\%$ ) and homogeneity (acceptable range  $\leq 10\%$  RSD) of the test article in the formulations were within the acceptable criteria with the exception of deviations in group 2 (0.001 mg/kg/day) for two formulations samples taken for homogeneity analysis on separate preparation days (10.3% and 13.1%). The formulation was stable for up to 15 days after preparation at 4°C and for at least one day at room temperature.

Toxicokinetics:

| Dose level<br>(mg/kg/day) | C <sub>max</sub><br>(ng/ml) | T <sub>max</sub><br>(h) | AUC <sub>last</sub><br>(ng.h/ml) |
|---------------------------|-----------------------------|-------------------------|----------------------------------|
| <b>GD 6</b>               |                             |                         |                                  |
| <b>0.01</b>               | 77.3                        | 4                       | 139                              |
| <b>0.1</b>                | 11.2                        | 8                       | 135                              |
| <b>1.0</b>                | 146                         | 4                       | 1150                             |
| <b>GD 18</b>              |                             |                         |                                  |
| <b>0.01</b>               | 1.17                        | 1                       | 6.39                             |
| <b>0.1</b>                | 17.4                        | 4                       | 170                              |
| <b>1.0</b>                | 138                         | 4                       | 1050                             |

- Mean  $C_{max}$  and mean  $AUC_{last}$  decreased from 0.01 mg/kg to 0.1 mg/kg, but increased from 0.1 mg/kg to 1.0 mg/kg on GD 6. On GD 18, mean  $C_{max}$  and mean  $AUC_{last}$  each increased with dosage in approximately dose-proportional relationships.
- There was no test article accumulation reported as a result of repeated dosing.
- Peak plasma concentrations ( $T_{max}$ ) were observed at 1-8 hours post dose.

*Maternal data:*

*Mortality and clinical observations:*

All rabbits survived to scheduled termination. There were no test article-related clinical observations.

*Body weight and Food consumption:*

- There were no test article-related effects on mean body weight and body weight gain at all dose levels.
- There was no test article-related effect on mean food consumption at all dose levels.

*Litter data:*

- There were no test article-related effects on litter parameters at all dose levels.

*Fetal Data:*

- There were no reported test article-related variations at all dose groups.
- At 1 mg/kg/day, the visceral malformations occurred in one fetus (VSD, constricted pulmonary artery and distended aorta were reported in one fetus).

**Conclusion:**

In contrast to the Applicant's conclusion stating that no fetal toxicity was observed at any dose level, this reviewer concludes that teratogenicity was evident at the highest dose assessed, 1 mg/kg/day. The reported visceral malformations at 1 mg/kg/day occurred in one fetus and were: interventricular septal defect (VSD), constricted pulmonary artery vessels and distended aorta. These findings were considered to be test article-related since in the dose-range study (Study number 311-006P) at 1 mg/kg/day dose, two fetuses from two different litters (2615-3 and 2616-2) were reported to have VSD's and fetus 2616-2 showed distended aorta and constricted pulmonary artery vessels.

Therefore, the NOAEL for embryo-fetal toxicity was established to be 0.1 mg/kg/day and the NOAEL for maternal toxicity was established to be greater than 1 mg/kg/day (no effects reported at the highest dose tested).

## 9 Special Toxicology Studies

### 9.1 Phototoxicity Studies

|                                         |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
|-----------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <p><b>Study<br/>#: 311-<br/>003</b></p> | <p><b>Title:</b> Ultraviolet Radiation and Visible Light Absorption Profile Study<br/><b>GLP:</b> Yes<br/><b>Objectives:</b> “The purpose of this study was to evaluate the ultraviolet radiation (UVR) and visible light absorption profile of tivozanib hydrochloride”.</p> <p><b>Methods:</b><br/>Tivozanib was suspended in 0.5% MC at concentrations of 0, 0.004, 0.04, 0.4, 4 and 40 mg/mL. These dilutions were evaluated spectrophotometrically in duplicate to determine which concentrations provided the best spectra. The test plate was scanned spectrophotometrically from 290 to 700 nm to determine if the vehicle possessed any absorption peaks. Isolation of the major peak was conducted at the 0.4 mg/mL concentration.</p> <p><b>Results:</b><br/>The majority of the light did not go through both suspensions of tivozanib (4 and 40 mg/mL). The 0.4 mg/mL dilution provided an average wave length of 329.5 nm (range 290 and 350 nm) and the highest absorption differential of 2.990. The 0.004 and 0.04 mg/mL were clear, however, the peak isolated at the 0.04 mg/mL concentration showed three peaks at approximately 293, 315 and 328 nm.</p> <p><b>Conclusion:</b><br/>The Applicant reported that the UVR and visible light absorption profile of tivozanib revealed strong absorbance in the UVR range from 290 through 340 nm with minimal absorption at wave lengths above 360. The peak absorbance occurred at approximately 329.5 nm. The peak isolated at the 0.04 mg/mL concentration showed three peaks at approximately 293, 315 and 328 nm.</p> |
| <p><b>Study<br/>#: 311-<br/>004</b></p> | <p><b>Title:</b> Single-Dose Phototoxicity Study to Determine the Effects on Eyes and Skin in Pigmented Rats</p> <p><b>GLP:</b> Yes</p> <p><b>Objectives:</b> “The purpose of this study was to determine the phototoxic effects on the eyes and skin of Long- Evans pigmented rats, after a single oral administration of tivozanib hydrochloride followed by exposures to radiation from a xenon lamp (to simulate sunlight)”.</p> <p><b>Methods:</b><br/>Animals: Long- Evans pigmented rats</p> <p><i>Study design:</i></p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |

| Group Number | Treatment Administration |                    |                          | Number of Animals |                  | Time between Dosing and UVR Exposure (hours) |
|--------------|--------------------------|--------------------|--------------------------|-------------------|------------------|----------------------------------------------|
|              | Treatment Article        | Dose Level (mg/kg) | Dosing Route and Regimen | Males             | Females          |                                              |
| 1            | (Vehicle) <sup>a</sup>   | 0                  |                          | 5                 | 5                |                                              |
| 2            |                          | 0.03               |                          | 5+5 <sup>b</sup>  | 5+5 <sup>b</sup> | 4 <sup>c</sup> , 24, 120                     |
| 3            | Tivozanib Hydrochloride  | 3                  | Single Oral Gavage       | 5                 | 5                |                                              |
| 4            |                          | 300                |                          | 5+5 <sup>b</sup>  | 5+5 <sup>b</sup> |                                              |
| 5            | 8-MOP                    | 50                 |                          | 5+5 <sup>b</sup>  | 5+5 <sup>b</sup> | 1                                            |

<sup>a</sup> Vehicle (0.5% methylcellulose).

<sup>b</sup> Due to formulations being found to be outside of specifications in Groups 2 and 4, an additional 5 rats/sex/group were assigned to a study extension where animals were dosed with the appropriate dose levels. An additional 5 rats/sex were included from Group 5 in the extension study. Results presented below are from Group 1 and 2 main study animals, Groups 2 and 4 extension study animals, and Group 5 main study animals.

<sup>c</sup> Skin exposure only. Skin and eyes were exposed at subsequent timepoints.

Note: Lot CDM-001 of tivozanib hydrochloride was used in this study. The dose levels are expressed in terms of the hydrated salt with no adjustment to free base. However, the dose levels were adjusted by purity (content).

8-MOP = 8-Methoxypsoralen; UVR = ultraviolet radiation.

(excerpted from Applicant's report)

One lightly and one darkly pigmented skin site was exposed to UVR approximately 4, 24, and 120 hours after formulation administration in rats in Groups 1- 4. In Group 5 rats, the eyes and the 2 skin sites were exposed to UVR approximately 1 hour after administration of 8-MOP.

Rats were examined for general appearance and general skin observations approximately 30 minutes after the completion of UVR exposure and 1, 2 and 3 days after UVR exposure. Rats were sacrificed and eyes were taken for histopathology evaluation.

**Results:**

- A female rat that received 300 mg/kg of tivozanib hydrochloride was found dead after UVR exposure on Day 2 of study.
- No test article-related skin toxicity reported at all dose levels tested.
- No test article-related ocular phototoxicity reported at all dose levels tested.
- There were no test article-related microscopic findings in the cornea, retina, sclera, iris, ciliary body, choroids, lens, aqueous and vitreous chambers, optic nerve and bulbar conjunctiva.

**Conclusions:**

A single oral administration of tivozanib followed by exposures to radiation from a xenon lamp did not elicit either skin or ocular findings indicative of phototoxicity in rats, at doses up to 300 mg/kg.

**10 Integrated Summary and Safety Evaluation**

*Pharmacology:* Tivozanib hydrochloride (referred to as KRN951, AV-951 or Tivozanib) is an anticancer agent of the vascular endothelial growth factor receptor (VEGFR) Tyrosine Kinase inhibitor class and is being developed for the treatment of advanced renal cell carcinoma. *In vitro* biochemical and cellular kinase assays demonstrated that tivozanib is an inhibitor of VEGF receptors (VEGFRs). In *in vitro* biochemical kinase assays, tivozanib inhibited the phosphorylation of VEGFRs-1, -2, and -3, with  $IC_{50}$  of 30, 6, and 15 nM, respectively, and inhibited other kinases at higher concentrations ( $IC_{50}$  ranging from 40 to 618 nM). In *in vitro* cell-based kinase assays, tivozanib inhibited the phosphorylation of VEGFRs-1, -2 and -3, with  $IC_{50}$  of 0.21, 0.16 and 0.24 nM (0.107, 0.081 and 0.122 ng/ml), respectively, and inhibited other kinases (C-kit and PDGFR $\beta$ ) at higher concentrations ( $IC_{50}$  of 1.63 and 1.72 nM, or 0.83 and 0.88 ng/ml, respectively). The VEGFR, C-kit and PDGFR $\beta$   $IC_{50}$  values are less than the  $C_{min}$  value achieved in RCC patients (16 to 30.9 ng/mL) following repeat dosing at the recommended dose of 1.5 mg/day, indicating that continuous inhibition of VEGF-mediated angiogenesis and activity of other identified kinases would be occurring during the treatment period.

In *in vivo* pharmacodynamic studies in mice and rats bearing human or murine xenograft tumors, tivozanib inhibited tumor growth via changes in angiogenesis and vascular permeability. In an oral repeat-dose study in nude rat xenograft models bearing 15 different human cancer cell lines, treatment with tivozanib (0.2 mg/kg/day; HED 1.95 mg/day) resulted in tumor growth inhibition (TGI  $\geq$ 50%) in 11 out 15 cell line models, and inhibition of intratumor angiogenesis, as was evident by the reduction in intratumor vascular endothelial cell density and vascular permeability. A similar outcome was reported in the repeat-dose studies in nude mice bearing murine breast HER2 xenograft tumors. Tivozanib treatment result in a decrease in viable tumor area, reduction in total number of proliferating cells, decrease in vessel cross-section area, decrease in microvascular density and an increase in tumor hypoxia, as measured by HIF1- $\alpha$  protein. The anti-tumor activity dose (0.2 mg/kg) in the rat model produced a mean  $C_{max}$  of 70 ng/ml (simulated serum concentration after repeat dosing) or 108 ng/ml and AUC of 1640 ng\*hr/ml following single dose. These plasma levels overlap those achieved in RCC patients following a repeat dosing at the recommended dose of 1.5 mg/day ( $C_{max}$  was 67.5 to 94.3 ng/mL and the  $AUC_{0-24}$  was 1180 to 1641 ng\*hr/mL, respectively).

In *safety pharmacology* studies, no effects on respiration rate, tidal volume, neurobehavioral endpoints or physiological parameters (Irwin test) were reported at 0.3 mg/kg in rat studies (HED=2.9 mg/day; 1.9-fold of the recommended human dose). The *in vitro* hERG tail-current study for tivozanib was designed with only a single concentration. As such, a concentration-response curve was not established (per ICHS7B), and the study provided no information regarding  $IC_{50}$ . Accordingly, this was not considered a valid study. An *in vivo* telemetry study was performed in male cynomolgus monkeys administered a single oral dose of tivozanib. The highest dose tested, 3 mg/kg (HED=54.4 mg/day; 38.9-fold of the recommended human dose) resulted in increases in systolic, diastolic and mean arterial blood pressure 90 minutes post dose. There were no test article-related effects on heart rates, RR, PR, QT, QTcF, QTcQ intervals and the QRS duration at any dose level. In an *in vivo* repeat-dose telemetry study in male

cynomolgus monkeys at doses of 1 or 3 mg/kg/day for 28 or 14 days, respectively, increases in systolic, diastolic and mean blood pressure were evident at 3 mg/kg/day. As such the results of the single- and repeat-dose telemetry study in monkeys at 3 mg/kg were consistent. At doses  $\geq$  1 mg/kg/day in the monkey, decreases in heart rate, cardiac output, renal arterial blood flow and cardiac arterial blood flow were reported. A decrease in vascular relaxation response and decrease in sensitivity to acetylcholine were also reported at doses  $\geq$  1 mg/kg/day (HED=19.5 mg/day; 13-fold of the recommended human dose), and may have played a role in the reported hypertension response in monkeys. Another possible cause of the increased blood pressure may be related to effects noted in the zona glomerulosa of the adrenal cortex (study # 6691-159; 13-week repeat-dose study in monkeys). Since the zona glomerulosa is responsible for the production of mineralocorticoids (e.g. aldosterone) which play a role in regulating blood pressure and kidney function, changes to this cell population may contribute to the observed physiological changes

*Pharmacokinetic studies:* *In vitro* and *in vivo* ADME studies were performed. Overall the data supported the use of rats and monkey in nonclinical studies, as these species would be expected to provide adequate coverage for potential human metabolites and associated toxicities.

- Tivozanib TK profile following oral administered was approximately linear in mice, rats and monkeys, with  $C_{max}$  and AUC increasing in an approximately dose proportional manner. No significant gender differences in exposure were reported. The rate of absorption was moderate and unaffected by dose level or duration of treatment in rats and monkeys, while, the rate of absorption ( $T_{max}$ ) and elimination half-life ( $t_{1/2}$ ) were different between species. The elimination  $t_{1/2}$  in rats (9-45 hours) was greater than that reported in monkeys (8-12 hours), but was considerably shorter than that reported for humans (4.5-5.1 days). As such, clinical regimen (QD, 3 weeks on and 1 week off) differs from the daily nonclinical dosing regimen, to account for these differences.
  - *Reviewer Note:* The toxicokinetics (TK) data supporting 10 toxicology studies was compromised due to data integrity issues and therefore are in non-compliance with the GLP regulations. The following reports were amended and data was discarded: 6691-158 (DRZZ1047), RCK0003, RZZ1008, RZZ1009, RZZ1010, RZZ1011, RZZ1012, RZZ1013, RZZ1014, and RZZ1015. As such, the data from these studies cannot be used to support this application, and were not reviewed.
- In *in vitro* distribution studies conducted using animal or human plasma, it was shown that the test article bound to plasma proteins at  $> 97.6\%$ , and protein binding was predominantly to albumin, with low binding to  $\alpha$ -1-acid glycoprotein. KRN951 mainly partitioned into the plasma/serum component of blood. Quantitative data on the tissue distribution of test article-related radioactivity in whole body of rats showed that the distribution of radioactivity was maximal at 4 hours post-dose. The highest radioactivity tissue concentrations were measured in the preputial gland, harderian gland, white fat and the liver. The concentrations in both the ovary and uterus were similar to the blood

levels, and those in testes were significantly less than in the blood. The majority of the radiation was eliminated from tissues at 24 hours post-dose, and by 72 hours post-dose the radiations levels were below the limit of quantification. In pigmented rats, melanin binding to the choroid layer of the eye was apparent and levels decreased steadily over 120 hours post-dose.

- *In vitro* and *in vivo* metabolism studies with KRN951 were performed and showed that in serum, the parent compound (KRN951) was the predominant circulating component (91% and 78% of the total radioactivity exposure in rat and monkey serum, respectively) with the metabolites M4 (mono-oxidation)/M5 (*N*-oxide of tivozanib) co-eluting and M63 in rats only. The parent compound was mainly detected in feces and only less than 0.5% in urine. In feces, the parent compound was the main component and other metabolites detected represented less than 5% of the administered radioactive dose. *In vitro* metabolism studies showed that KRN951 metabolism was low in all species studied, as was evident by the low hepatic clearance, and that KRN951 appeared to be metabolized mainly by oxidation and demethylation. All prominent human metabolites (M1 through M24) were present in both rat and monkey with the exception of M11 (glucuronide), which was unique to human hepatocytes (minor >0.5%) and M10 which was not observed with rat hepatocytes. M14 was present at >10% of total radioactivity and was designated as a major metabolite in human, monkey and rat. Comparison of the metabolic profile of tivozanib in human, monkey, dog and rat liver microsomes showed that monkey is the closest to human followed by the rat, and dog was determined to be the most different. CYP3A4 and CYP1A1 are the major human hepatic CYP isoform involved in the metabolism of tivozanib.
- In rats and monkeys the main excretion route was through the feces, and to a smaller extent (2-3%) through urine. Excretion through the bile duct was identified in rats.

*In genetic toxicology studies:* Tivozanib was not considered mutagenic in the *in vitro* reverse mutation assay (Ames) or aneugenic in the *in vivo* clastogenicity assay in rodents. In addition, tivozanib was not considered clastogenic in the *in vitro* mammalian cell cytogenetic test; however, tivozanib produced changes in chromosomal number (polyploidy, hyperdiploidy) at doses  $\geq 2 \mu\text{g/mL}$  (1.2-fold the plasma level at the recommended human dose).

*Impurity qualification:* The potential impurities of the tivozanib drug substance were evaluated and eight out of 39 of the compounds were found to be positive in Ames; these included (b) (4) [redacted]. There were two impurities identified to be above the ICH qualification threshold: (b) (4) [redacted] in Drug Substance and (b) (4) [redacted] in Drug Product), but given that levels of these impurities at doses that did not result in severe toxicity in nonclinical studies were higher than the maximum potential doses of these impurities in patients if they were at the levels of the specifications, the impurity specifications were considered qualified by the nonclinical data. The maximum amount of (b) (4) [redacted]

a genotoxic impurity, administered to patients will be <sup>(b) (4)</sup> μg/day, which is acceptable for the indicated patient population.

*Reproductive toxicology:* In male and female fertility studies, systemic toxicity was reported (clinical observations and decreases in body weight and food consumption) at doses  $\geq 0.1$  mg/kg/day (HED=0.97 mg/day; 0.64-fold of the recommended human dose). At doses  $\geq 0.1$  mg/kg/day mating was affected as evident by the increase in number of days in cohabitation, and decrease in number of male and female rats that mated. Doses  $\geq 0.3$  mg/kg/day affected the fertility index (number of pregnancies per number of rats mated) as evident by the decrease in number of rats pregnant per rats in cohabitation. As such, the NOAEL was established to be 0.1 mg/kg/day (HED=0.97 mg/day; 0.43-fold of the recommended human dose). In the embryo-fetal developmental study in rats, tivozanib was administered orally throughout organogenesis. Maternal toxicity, increases in resorptions (early and late), fetal external malformations (body edema, short tail and kinked tail) and skeletal developmental delays were reported at doses  $\geq 0.03$  mg/kg/day (HED=0.29 mg/day; 0.19-fold of the recommended human dose). A NOAEL for maternal and embryo-fetal toxicity was established to be 0.01 mg/kg/day (HED=0.097 mg/day; 0.06-fold of the recommended human dose). In the rabbit embryo-fetal developmental study, pregnant rabbits were dosed orally throughout organogenesis. There was no reported maternal toxicity at any dose. Embryo-fetal toxicity was evident at 1 mg/kg/day (VSD, constricted pulmonary artery vessels and distended aorta). The NOAEL for maternal toxicity was established to be greater than 1 mg/kg/day (HED=19.5 mg/day; 13-fold of the recommended human dose), while the NOAEL for embryo-fetal toxicity was established to be 0.1 mg/kg/day (HED=0.19 mg/day; 1.3-fold of the recommended human dose).

*Single-dose toxicology:* The maximum tolerated dose in mice and rats following a single IV administration was established to be greater than the highest dose tested of 30 mg/kg. This dose was established as the maximum feasible dose. Given that the oral route is the proposed clinical route, the studies used to assess the safety of the compound in support of the current NDA application were conducted using the oral route as follows. The MTDs for a single oral dose in mice and rats were 524 mg/kg and 276 mg/kg, respectively (1700 and 1790-fold of the recommended human dose). These doses resulted in body weight decrease, an increases in ALT, AST and ALP, an increase in hematology parameters (red blood cells, hemoglobin, hematocrit, and neutrophils), and decreases in lymphocyte and total white blood cell counts.

*Repeat-dose toxicology:* **Rats** were orally dosed with tivozanib for 13 weeks (0.01, 0.03, 0.1, 0.3, or 1.0 mg/kg/day) and 26 weeks (0.005, 0.02 or 0.08 mg/kg/day). In the 13-week study, doses  $\geq 0.1$  mg/kg/day resulted in mortalities and severe clinical observations (clinical signs typically associated with morbidity, malocclusion, missing teeth and white teeth) with effects more pronounced at 1 mg/kg/day, resulting in cessation of dosing at 1 mg/kg/day after 4 weeks of dosing. The malocclusion and missing teeth findings were correlated with microscopic findings in the incisors (degeneration of odontoblasts, ameloblasts and dentin dysplasia) and may have contributed to the body weight and food consumption decreases reported at doses  $\geq$

0.03 mg/kg/day. The dental toxicity in rats was not observed in monkeys, likely because this effect is a direct effect on growing teeth. In rats, growth of the incisors is continuous throughout the entire lifespan of the animal, which is different from monkey and human. Therefore, the effect on incisors is unlikely to be relevant to the targeted patient population (adults) for this indication. The reported decreases in body weights and food consumption were accompanied by test article-related changes in clinical pathology parameters. The hematology parameters reported at doses  $\geq 0.03$  mg/kg/day included decreased red blood cell parameters, and at doses  $\geq 0.1$  mg/kg/day included increased white blood cell parameters. Clinical chemistry changes included increase in iron metabolism at doses  $\geq 0.03$  mg/kg/day; decrease in protein parameters and increase in liver parameters at doses  $\geq 0.1$  mg/kg/day; and increases in LDH/creatinine, triglycerides and renal parameters at 1 mg/kg/day. Test article-related urinalysis changes were reported at doses  $\geq 0.1$  mg/kg/day (increased protein); at doses  $\geq 0.3$  mg/kg/day (increased urobilinogen and bilirubin) and at 1 mg/kg/day (increased hyaline casts). Test article-related macroscopic findings and organ weights were reported in multiple organs in both sexes at doses  $\geq 0.01$  mg/kg/day. Macroscopic and microscopic findings were reported at doses  $\geq 0.1$  mg/kg/day in both sexes. In general, the incidence and/or severity of the findings were dose-dependent. At doses  $\geq 0.1$  mg/kg/day the target organs with significant toxicity observed were adrenal glands, kidney (correlated with an increases in uribilinogen, and other proteins), bone femur, liver (correlated with the increase in the levels of liver parameters such ALT, U GGT, total bilirubin, LDH and triglycerides) and bile duct, brain, pituitary, incisors, pancreas and duodenum. Less pronounced (lower incidence and/or severity) microscopic findings were reported in the heart, reproductive organs, bone marrow, adrenal medulla and stomach. Similar microscopic findings in bone, pancreas and incisors were reported in the 4-week repeat dose study in rats (study # RZZ1013). The NOAEL was considered to be 0.03 mg/kg/day (HED = 0.29 g/day; 0.2-fold of the recommended human dose) based on adverse microscopic findings. Toxicities at doses  $\geq 0.3$  mg/kg/day were severe and for the most part were not recoverable. Partial recovery of most effects was reported at doses  $\geq 0.1$  mg/kg/day, although renal effects were not recoverable at these doses. In the 26-week rat study, findings of white teeth (doses  $\geq 0.005$  mg/kg/day), decrease in body weight, hematology findings (increases in leukocytes, hemoglobin, hematocrit and erythrocytes) and clinical chemistry findings (decreases in total protein, albumin and globulins in both sexes) were reported at 0.08 mg/kg/day. The above observed effects were not considered to be adverse, and no additional test article-related findings were reported by the end of the treatment or the recovery periods. The NOAEL was established to be the highest dose tested, 0.08 mg/kg/day (HED = 0.78g/day; or 0.5-fold the recommended human dose).

In the repeat-dose toxicology studies, **monkeys** were orally dosed with tivozanib for 13 weeks (0.01, 0.03, 0.1, 0.3 or 1 mg/kg/day) and 39 weeks (0.005, 0.01, 0.02, 0.03 or 0.08 mg/kg/day). In the 13-week monkey study, a dose of 1.0 mg/kg was considered severally toxic, and therefore, dosing was ceased after approximately 4 weeks of dosing. Doses  $\geq 0.3$  mg/kg/day resulted in clinical signs and decrease in body weights. Test article-related hematological changes were evident at 1 mg/kg/day (increases in RBC parameters, fibrin and M/E ratio; decreases in WBC, RETIC, NEUT, MCV and PT). Test article-related clinical and urine chemistry changes were evident at 1 mg/kg/day (increases in CK, SELA- $\alpha$  &  $\beta$ , iron,

phospholipids; decreases in ALP, SDH, total bile acid, amylase, UIBC, U LDH, U creatinine). The clinical chemistry changes reported at doses  $\geq 0.1$  mg/kg/day (increases in SELA- $\alpha$ , CK, and phospholipids) were considered test article-related, but changes were of lesser magnitude. Some of clinical pathology changes were attributed to the reported body weight changes. At doses  $\geq 0.3$  mg/kg/day, significant decreases in absolute and relative thymus weights was reported. Macroscopic findings were only evident at 1 mg/kg/day. At doses  $\geq 0.1$  mg/kg/day, microscopic findings in the brain and adrenal cortex were reported. The predominant test article-related microscopic findings evident at doses  $\geq 0.3$  mg/kg/day included bone (femur and tibia), gastric system (stomach, duodenum and pancreas), reproductive system (ovary and corpora lutea), and lymphoid depletion of lymphoid organs (thymus, lymph nodes and spleen). Similar microscopic findings in bone, pancreas and thymus were reported in the 4-week repeat dose study in monkeys (study # RZZ1015). The majority of the findings in the 13-week study were recoverable after a 2- or 5-week recovery period. The NOAEL was established to be 0.1 mg/kg/day (HED = 1.95 g/day; 1.3-fold of the recommended human dose). In a 39-week monkey study, the highest dose tested (0.1 mg/kg/day) was well tolerated. No test article-related clinical observations were reported. There were no effects on body weight, clinical pathology, echocardiographic, ECG, macro and microscopic findings reported at all dose levels. The NOAEL was established to be 0.1 mg/kg/day (HED=1.95 g/day; 1.3-fold of the maximum recommended human dose).

- *Discussion of toxicities:* Of note was that in the monkey study, the ossification findings were limited to bone. Given that teeth do not grow at a constant rate in monkeys, the incisor findings in the rat study were not present in the monkey studies. The growth plate hypertrophy effect on the femur and/or tibia in the rat and monkey is an important finding, and would be a significant safety concern in young/young adult populations, as the epiphyseal plate remains active until the age of  $\sim 20$  years in the human. Given the targeted age patient population for tivozanib, the bone toxicities may not be relevant. In the monkey, microscopic findings in the adrenal cortex were observed in the zona glomerulosa. This tissue is responsible for the production of mineralocorticoids (e.g. aldosterone) that plays a role in regulating blood pressure and kidney function, and as such may contribute to the blood pressure and renal function changes reported in the cardiovascular safety pharmacology study in monkeys.

Overall both the 26-week rat and 39-week monkey toxicology studies were insufficient, as the highest dose(s) assessed produced no/minimal toxicity and dose-response relationships could not be evaluated. Given the low safety margin noted for this study in regard to the clinical dose, it is uncertain why the Applicant did not explore a more robust range of doses in these studies. Given the lack of substantial toxicity in these studies, the Applicant uses the data from the 13-week rat and monkey studies to inform the label regarding acute toxicities.

*Phototoxicity studies:* Ocular and cutaneous phototoxicity studies with tivozanib in rats did not show cutaneous or ocular phototoxicity.

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/s/  
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EIAS A ZAHALKA  
05/24/2013

TODD R PALMBY  
05/24/2013

#### **19.4 OCP Appendices (Technical documents supporting OCP recommendations)**

As mentioned above, tivozanib has been reviewed by the Office of Clinical Pharmacology under NDA 204408 in 2012-2013. Only two more clinical studies were included in current submission, the dedicated hepatic impairment study AV-951-12-118 and the pivotal study AV-951-15-303 (TIVO-3). Therefore, the current review had an overview of the clinical pharmacology characteristics of tivozanib and focused on the intrinsic factors that may influence exposure.

##### **19.4.1 Summary of Bioanalytical Method Validation and Performance**

###### **Were relevant metabolite concentrations measured in the clinical pharmacology and biopharmaceutics studies?**

Yes. Unchanged tivozanib is the predominate circulating product in serum with no major active metabolites. Therefore, only tivozanib was measured in the clinical pharmacology and biopharmaceutics studies.

###### **For all moieties measured, is free, bound, or total measured? What is the basis for that decision, if any, and is it appropriate?**

The total plasma concentration of tivozanib was measured in the clinical trials. This was appropriate as tivozanib is greater than 99% plasma protein bound over the clinically relevant concentration range studied.

###### **What bioanalytical methods are used to assess concentrations?**

Method TVZHSP (Validation Report: 8253837) is an LC-MS/MS method for the determination of tivozanib (also known as AV951, AV-951, and KRN951) in human serum using a liquid-liquid extraction method. KRN633 (also known as CDU) was used as the internal standard.

Concentrations were calculated with a 1/x linear regression over a concentration range of 0.100

(LLOQ) to 100 ng/mL (ULOQ) with 9 calibration standards. This method was used in study AV-951-15-303 (also known as TIVO-3; Report 8333396) and study AV-951-12-118.

Method TVZHSP was based on a method developed by (b) (4). The method was validated at (b) (4) as Method TVZHSP and sample analysis for studies TIVO-3 and AV-951-12-118 were completed in their entirety at (b) (4). Method validation assessments for TVZHSP included precision, accuracy, sensitivity, matrix effect, recovery, carryover, dilution integrity, and the relevant stability parameters. A summary of the results is included in the table below.

Table 1: Method TVZHSP Summary

|                                     |                                                                                                                                                                                                                              |      |                    |
|-------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------|--------------------|
| Sample Volume                       | 100 µL                                                                                                                                                                                                                       |      |                    |
| Regression                          | linear                                                                                                                                                                                                                       |      |                    |
| Weighting factor                    | 1/x                                                                                                                                                                                                                          |      |                    |
| Dynamic Range                       | 0.100 - 100 ng/mL                                                                                                                                                                                                            |      |                    |
| QC concentrations                   | 0.250, 4.00, 75.0 ng/mL                                                                                                                                                                                                      |      |                    |
| Analyte                             | tivozanib                                                                                                                                                                                                                    |      |                    |
| Internal Standard                   | KRN633                                                                                                                                                                                                                       |      |                    |
| Linearity                           | $R^2 \geq 0.9985$                                                                                                                                                                                                            |      |                    |
| Lower limit of quantitation         | 0.100 ng/mL                                                                                                                                                                                                                  |      |                    |
| Average % recovery of Analyte       | 101.2%                                                                                                                                                                                                                       |      |                    |
| QC Level                            |                                                                                                                                                                                                                              | LLOQ | Low, Mid, and High |
| QC Intra-Run Precision Range (%RSD) | Run 2                                                                                                                                                                                                                        | 5.3  | 2.2 - 2.9          |
|                                     | Run 4                                                                                                                                                                                                                        | 7.2  | 0.9 - 3.2          |
|                                     | Run 5                                                                                                                                                                                                                        | 7.5  | 1.9 - 3.3          |
| QC Intra-Run Accuracy Range (%Bias) | Run 2                                                                                                                                                                                                                        | -9.4 | -0.4 - 1.8         |
|                                     | Run 4                                                                                                                                                                                                                        | 3    | 0.8 - 1.3          |
|                                     | Run 5                                                                                                                                                                                                                        | -6.7 | 2.4 - 10.0         |
| QC Inter-Run Precision Range (%CV)  |                                                                                                                                                                                                                              | 8.6  | 2.9 - 4.5          |
| QC Inter-Run Accuracy (% Accuracy)  |                                                                                                                                                                                                                              | -4.4 | 1.2 - 4.5          |
| Dilution Integrity                  | 400 ng/mL diluted at 1:50 with %RSD = 3.5 and %Bias = 3.3                                                                                                                                                                    |      |                    |
| Matrix Factor                       | IS normalized matrix factor of $0.973 \pm 0.0347$ at 0.250 ng/mL with %RSD = 3.6                                                                                                                                             |      |                    |
| Batch Size                          | 96 samples                                                                                                                                                                                                                   |      |                    |
| Selectivity                         | In all cases, the tivozanib and KRN633 regions were free from significant interference ( $\leq 20.0\%$ of the response from the single LLOQ used and $\leq 5.0\%$ of internal standard response in the control zero sample). |      |                    |

|                                 |                                                                                                                                                                                                                                                                                        |
|---------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Carryover                       | The extracts of blank matrix demonstrated a lack of significant carryover in the chromatographic regions of interest for tivozanib ( $\leq 20.0\%$ of the response from the single LLOQ used) and KRN633 ( $\leq 5.0\%$ of the internal standard response in the control zero sample). |
| QC Sample Bench Top Stability   | 29 hours at room temperature                                                                                                                                                                                                                                                           |
| Processed Sample Stability      | 96 hours                                                                                                                                                                                                                                                                               |
| Reinjection Reproducibility     | 96 hours                                                                                                                                                                                                                                                                               |
| QC sample Freeze/Thaw Stability | 5 cycles at $-20\text{ }^{\circ}\text{C}$ and $-70\text{ }^{\circ}\text{C}$                                                                                                                                                                                                            |
| Long Term Stability             | 566 days at $-70\text{ }^{\circ}\text{C}$ ; 1686 days at $-20\text{ }^{\circ}\text{C}$                                                                                                                                                                                                 |

A total of 13 runs were performed using method TVZHSP during sample analysis of TIVO-3. The precision of the QC samples was  $-2.5$  to  $-0.3\%$  and the accuracy was  $97.5$  to  $99.8\%$ . A total of 23 samples were repeated due to the original result of tivozanib being above the limit of quantitation ( $100\text{ ng/mL}$ ). Samples were diluted up to  $1:10$ , which was within the validated dilution range. Incurred sample reanalysis for tivozanib was performed on 32 samples and passed acceptance criteria since  $100\%$  of the ISR samples had a percent difference from the original result of less than  $20\%$ .

A total of 17 runs were performed using method TVZHSP during sample analysis of AV-951-12-118. The precision of the QC samples was  $1.5$  to  $7.3\%$  and the accuracy was  $98.9$  to  $110.8\%$ . A total of 8 samples were repeated due to a positive pre-dose ( $2/8$  samples), re-assay to confirm results ( $5/8$  samples), and pharmacokinetic repeat ( $1/8$  samples). Incurred sample reanalysis for tivozanib was performed on 72 samples and passed acceptance criteria since  $99\%$  of the ISR samples had a percent difference from the original result of less than  $20\%$ .

#### 19.4.2 Clinical PK

Seven clinical pharmacology Phase 1 studies have been completed to characterize the PK of oral tivozanib; six have been completed in healthy or hepatically impaired volunteers (Studies AV-951-10-111, AV-951-10-115, AV-951-11-116, AV-951-11-117, AV-951-12-118 and AV-951-09-109) and one in patients with advanced solid tumors (Study AV-951-10-112). An additional six clinical monotherapy studies conducted in patients with solid tumors also included PK endpoints (Studies AV-951-03-B01, AV-951-08-105, AV-951-07-201, AV-951-10-202, AV-951-09-301, and AV-951-15-303).

A summary of these trials and their top-line findings is provided in Table 2 below.

|                                                                    |
|--------------------------------------------------------------------|
| Table 2. Summary of Clinical Pharmacology Study Design and Results |
|--------------------------------------------------------------------|

NDA/BLA Multi-disciplinary Review and Evaluation {NDA 212904}  
 {FOTIVDA, tivozanib}

| Study ID                             | Study Design                                                                                                                                                              | Key Inclusion/Exclusion Criteria                                                                                                | PK/PD Endpoint                                                                                                              | Number of Subjects per Dose                                    | Schedule/Route of Administration                                                                                                                                                                                                                                                                               | Status/Timing of Study                             | Key Findings                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
|--------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Clinical Pharmacology Studies</b> |                                                                                                                                                                           |                                                                                                                                 |                                                                                                                             |                                                                |                                                                                                                                                                                                                                                                                                                |                                                    |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
| AV-951-10-111                        | Phase 1, open-label investigation of the absorption, metabolism, and excretion of a single dose of [ <sup>14</sup> C]-tivozanib in healthy male volunteers                | Healthy adult male subjects (18 to 55 years of age) inclusive; with a BMI range of 18.5 to 31.0 kg/m <sup>2</sup> , inclusive   | Assess the PK of a single 1.5 mg (160 µCi) dose of tivozanib and its metabolites using [ <sup>14</sup> C]-labeled tivozanib | 8 enrolled<br>7 completed<br>Tivozanib<br>1.5 mg               | Single oral dose of [ <sup>14</sup> C]-tivozanib                                                                                                                                                                                                                                                               | Completed<br>FSD:<br>Jun 2010<br>LSV:<br>Jul 2010  | Following a single oral dose of 1.5 mg radiolabeled tivozanib, [ <sup>14</sup> C]-tivozanib was slowly absorbed (median T <sub>max</sub> = 10.0 hours) in serum, with a demonstrated long terminal half-life (mean t <sub>1/2</sub> = 89.3 hours). The majority (mean 79.3%) of [ <sup>14</sup> C]-tivozanib was excreted in the feces as both unchanged tivozanib and metabolites, while the remainder (mean 11.8%) was excreted as metabolites in urine.                                                                                                                                                                                                                                                                                                                         |
| AV-951-10-112                        | Phase 1, open-label, non-randomized, exploratory single-arm trial evaluating the ECG and PK-ECG relationship, if any, of tivozanib in subjects with advanced solid tumors | Male and female subjects ≥ 18 years of age, with advanced solid tumors and an ECOG PS of 0 or 1, and life expectancy ≥ 3 months | To determine the relationship, if any, of the change in QTcF duration with serum concentration of tivozanib over time       | 51 enrolled<br>50 dosed<br>Tivozanib<br>1.5 mg                 | Tivozanib orally once daily for 21 days                                                                                                                                                                                                                                                                        | Completed<br>FSD:<br>Oct 2010<br>LSV:<br>Mar 2011  | At C <sub>max</sub> predicted mean change was 8.3 ms (UCI: 12.6 ms) increase in QTcF duration using the exposure-effect model. Maximum mean change in QTcF was 9.3 ms (90% CI: 5, 13.6) occurring 2.5 hours after dose on Day 21. The central tendency change across all time points was 2.2 ms.<br><br>The slope for QTcF was 0.08464 indicating a small exposure- effect relationship, with an estimated QTcF change at C <sub>max</sub> of 8.2694, (UCI of 12.6493).<br><br>The results of the ECG analysis revealed that tivozanib was correlated with a slight reduction in heart rate of no clinical meaningfulness. There was no significant effect on PR interval, a 2.1 ms increase in the QRS duration, and new morphological ST-T changes were noted in a few subjects. |
| AV-951-10-115                        | Phase 1, single center, open-label, randomized, two-period crossover food effect study of single doses of tivozanib in healthy volunteers                                 | Healthy male and female subjects aged 18 to 55 years, inclusive; with a BMI range of 18.5 to 31.0 kg/m <sup>2</sup> , inclusive | Determine the effect of food on the PK of a single dose of 1.5 mg tivozanib in healthy volunteers                           | 30 enrolled (15 per treatment sequence)<br>Tivozanib<br>1.5 mg | One of 2 treatment sequences:<br>1: Treatment A → Washout → Treatment B<br>2: Treatment B → Washout → Treatment A<br>Treatment A: single oral dose of tivozanib after an approximate 10-hour fast<br>Treatment B: single oral dose of tivozanib following consumption of a standardized FDA high fat breakfast | Completed<br>FSD:<br>Feb 2011;<br>LSV:<br>May 2011 | An approximately 23% (arithmetic mean) decrease in C <sub>max</sub> in the fed condition compared to the fasted condition was found. The decrease in C <sub>max</sub> was statistically significant with the 90% CI for C <sub>max</sub> was not entirely within the 80% to 125% range, generally considered indicative of bioequivalence. Food did not have an effect on the mean AUC <sub>0-4</sub> and AUC <sub>0-∞</sub> and the 90% CIs for AUCs were entirely contained within the 80% to 125% range. The half-life, CL/F, and apparent Vz/F were similar between fed and fasted conditions.                                                                                                                                                                                 |

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|               |                                                                                                                                                                                 |                                                                                                                                                   |                                                                                                                                                            |                                                                                                          |                                                                                                                                                                                                                                                    |                                                   |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
|---------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| AV-951-11-116 | Phase 1, open-label investigation of the effect of ketoconazole on the PK, safety, and tolerability of a single dose of tivozanib in healthy volunteers                         | Healthy male and female subjects aged 18 to 55 years, inclusive; with a BMI range of 18.5 to 31.0 kg/m <sup>2</sup>                               | Examine the effect of steady-state ketoconazole on the PK of a single dose of 1.5 mg of tivozanib in healthy volunteers                                    | 30 enrolled<br>25 completed<br>Tivozanib: 1.5 mg<br><br>Ketoconazole: 400 mg (2 x 200-mg tablets)        | Period 1: oral tivozanib administered after a 10-hour fast.<br><br>Period 2: Once daily doses of oral ketoconazole on Day 37 to Day 61, coadministered with oral tivozanib on Day 40                                                               | Completed<br>FSD:<br>May 2011<br>LSV:<br>Jul 2011 | Administration of tivozanib in the presence of steady-state ketoconazole concentrations did not cause a clinically significant change in the PK of tivozanib. The LS tivozanib C <sub>max</sub> concentration was approximately 3% lower and AUC <sub>0-4</sub> and AUC <sub>0-∞</sub> values were approximately 9% and 5% higher, respectively, after administration of tivozanib with ketoconazole compared to tivozanib alone. However, the 90% CIs for C <sub>max</sub> , AUC <sub>0-4</sub> , and AUC <sub>0-∞</sub> LS ratios were entirely contained within the 80% to 125% bioequivalence range. |
| AV-951-11-117 | Phase 1, open-label investigation of the effect of rifampin on the PK, safety, and tolerability of a single dose of tivozanib in healthy volunteers                             | Healthy male and female subjects aged 18 to 55 years, inclusive; with a BMI range of 18.5 to 31.0 kg/m <sup>2</sup>                               | Examine the effect of steady-state rifampin on the PK of a single 1.5 mg tivozanib dose in healthy volunteers                                              | 30 enrolled<br>27 completed<br>Tivozanib: 1.5 mg<br><br>Rifampin: 600 mg                                 | Period 1: 1.5 mg oral tivozanib administered after a 10-hour fast.<br><br>Period 2: Once daily doses of oral rifampin on Day 36 to Day 63, coadministered with oral tivozanib on Day 42                                                            | Completed<br>FSD:<br>May 2011<br>LSV:<br>Jul 2011 | Coadministration of tivozanib with steady-state concentrations of rifampin had a statistically significant effect on the exposure of tivozanib, with decreases in geometric mean AUC <sub>0-4</sub> and AUC <sub>0-∞</sub> values of approximately 50%. The 90% CIs of AUC <sub>0-4</sub> and AUC <sub>0-∞</sub> of tivozanib were all outside the equivalence range, while the 90% CI of C <sub>max</sub> was within the 80% to 125% range.                                                                                                                                                             |
| AV-951-12-118 | A Phase 1, open-label, single dose study to evaluate the pharmacokinetics, safety and tolerability of tivozanib in subjects with hepatic impairment and normal hepatic function | Male and female subjects 18 to 75 years of age, inclusive; BMI range of 18 to 38 kg/m <sup>2</sup> , inclusive with or without hepatic impairment | Compare the PK of a single 1.5 mg dose of tivozanib in subjects with mild, moderate and severe hepatic impairment to subjects with normal hepatic function | Approximately 44 subjects were planned; 44 subjects were enrolled and analyzed.<br><br>Tivozanib: 1.5 mg | Single 1.5 mg oral dose of tivozanib on Day 1                                                                                                                                                                                                      | Completed<br>FSD:<br>May 2012<br>LSV<br>Aug 2013  | Across the entire measurement period, tivozanib was eliminated more slowly in subjects with moderate or severe hepatic impairment.<br><br>Results suggest a dose adjustment is warranted in subjects with moderate hepatic impairment. Use of tivozanib is not suggested for those with severe hepatic impairment                                                                                                                                                                                                                                                                                        |
| AV-951-09-109 | Phase 1, open-label, single center, randomized, two-period, two-treatment, crossover bioequivalence study of single doses of tivozanib in healthy volunteers                    | Healthy male or female, non-smoking, age 18 to 55 years, with a BMI range of 19 to 31 kg/m <sup>2</sup>                                           | Assess the bioequivalence of tivozanib administered as a tablet formulation and administered as a capsule formulation                                      | 34 enrolled<br>34 completed<br><br>Sequence A/B (n = 17)<br>Sequence B/A (n = 17)                        | One of 2 treatment sequences:<br>1: Treatment A → Washout → Treatment B<br>2: Treatment B → Washout → Treatment A<br><br>Treatment A: single oral dose of tivozanib 1.5 mg tablet<br><br>Treatment B: single oral dose of tivozanib 1.5 mg capsule | Completed<br>FSD:<br>May 2009<br>LSV:<br>Nov 2009 | Treatment A (1.5 mg tivozanib tablet) was bioequivalent to Treatment B (1.5 mg tivozanib capsule).                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |

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| Other Clinical Studies with Pharmacokinetic Endpoints |                                                                                                                                 |                                                                                                                                                                                                              |                                                                                                                      |                                                                                                                                                                                                                          |                                                                                                                                                                  |                                                   |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
|-------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Monotherapy                                           |                                                                                                                                 |                                                                                                                                                                                                              |                                                                                                                      |                                                                                                                                                                                                                          |                                                                                                                                                                  |                                                   |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
| Study ID                                              | Study Design                                                                                                                    | Key Inclusion/Exclusion Criteria                                                                                                                                                                             | PK/PD Endpoint                                                                                                       | Number of Subjects per Dose                                                                                                                                                                                              | Schedule/Route of Administration                                                                                                                                 | Status/Timing of Study                            | Key Findings                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
| AV-951-03-B01                                         | Phase 1, safety, tolerability, MTD, PK, and PD. Open-label, non-randomized, dose escalation                                     | Adult subjects with histologically or cytologically confirmed, unresponsive, untreatable, solid tumors; life expectancy $\geq 3$ months; and ECOG PS $\leq 2$                                                | Determine the PK of tivozanib and VEGF-A and soluble VEGFR-2 levels in serum                                         | 42 enrolled<br>42 treated<br>Tivozanib<br>1.0 mg = 18<br>1.5 mg = 16<br>2.0 mg = 7 <sup>a</sup>                                                                                                                          | Orally, once daily for 28 days followed by a 14-days with no treatment                                                                                           | Completed<br>FSD:<br>Mar 2004<br>LSV:<br>Feb 2010 | Tivozanib PK was characterized by a serum concentration profile with no discernable terminal elimination phase during a 24-hour dosing interval, high inter-subject variability in serum concentrations, and approximately, although not statistically, dose-proportionate exposure. In addition, PD analyses of serum levels of VEGF-A showed dose-dependent increases. Analyses of serum levels of sVEGFR-2 showed dose-dependent decreases.                                                                                                                                                                                                                                                   |
| AV-951-08-105                                         | Phase 1b multicenter study to evaluate the safety and activity of tivozanib in subjects with NSCLC. Open-label, dose escalation | Adult subjects with histologically or cytologically confirmed NSCLC                                                                                                                                          | Evaluate the PK of tivozanib                                                                                         | Phase 1b:<br>17 enrolled<br>17 completed<br>Tivozanib<br>1.0 mg = 9<br>1.5 mg = 8                                                                                                                                        | Orally, once daily continuously                                                                                                                                  | Completed<br>FSD:<br>Mar 2009<br>LSV:<br>Feb 2011 | The observed trough serum concentrations of tivozanib were dose dependent and approximated steady state by Cycle 1 Day 15.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
| AV-951-07-201                                         | Phase 2, safety, tumor activity, progression-free survival, PK and PD. Placebo-controlled, randomized, discontinuation trial    | Adult subjects with recurrent or metastatic RCC, or primary RCC not amenable to surgery; KPS $\geq 70\%$ ; life expectancy $\geq 3$ months                                                                   | Characterize the PK profiles of tivozanib in a subset of subjects. Serum biomarker levels (VEGF and sVEGFR-2 levels) | 274 enrolled<br>272 dosed<br>Tivozanib<br><br>1.5 mg <sup>b</sup> for 16 weeks, then either:<br>continue open-label randomization to tivozanib or matching placebo, or DC<br><br>PK/PD subset = 21 subjects from 3 sites | Orally, once daily for 21 days followed by 7 days with no treatment.                                                                                             | Completed<br>FSD:<br>Oct 2007<br>LSV:<br>Aug 2010 | The serum concentration-time profile of tivozanib was relatively flat with no discernable terminal elimination phase over the measured interval. Serum concentrations were highly variable between subjects, making it difficult to determine when steady state occurred. Based on the estimated mean $t_{1/2}$ (87 hours), steady state should be reached after $\sim 12$ days.<br><br>As estimated by the mean ratio of AUC during a dosing interval (24 hours) on Day 21 and Day 1, the accumulation of tivozanib at steady state was about 7-fold that of a single dose.<br><br>VEGF levels rapidly increased following tivozanib treatment, with a concomitant decrease in sVEGFR-2 levels. |
| AV-951-10-202                                         | Phase 2, biomarker, progression-free survival, safety, and PK. Open-label trial                                                 | Adult subjects with histologically or cytologically confirmed advanced RCC (unresectable locally recurrent or metastatic) with a clear cell component, ECOG PS of 0 or 1 and life expectancy $\geq 3$ months | Correlate biomarker measures and serum concentrations of tivozanib (biomarker evaluation not done)                   | 105 enrolled and dosed                                                                                                                                                                                                   | 1.5 mg oral tivozanib once daily for 3 weeks followed by 1 week off study drug (1 cycle = 4 weeks [3 weeks on, 1 week off]). Cycles were repeated every 4 weeks. | Completed<br>Aug 2012                             | Trough serum concentration measurements suggest that tivozanib had reached steady-state concentrations by 14 days after the first dose. Observations obtained after a 7-day rest showed that significant concentrations of tivozanib persisted during the 7-day drug holiday. Results are consistent with previously observed PK data for tivozanib trough concentrations with daily dosing.                                                                                                                                                                                                                                                                                                     |

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|               |                                                                                                                                           |                                                                                                                                                      |                                                                             |                                                                                                         |                                                                                                                                                                                                                            |                              |                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
|---------------|-------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| AV-951-09-301 | Phase 3, randomized, controlled, multicenter, open-label study to compare tivozanib to sorafenib in subjects with advanced RCC            | Adult subjects with histologically or cytologically confirmed RCC with a clear cell component, ECOG PS of 0 or 1 and life expectancy $\geq 3$ months | Evaluate the PK of tivozanib                                                | 517 enrolled<br>516 dosed<br>Tivozanib 260 enrolled<br>259 dosed<br>Sorafenib 257 enrolled<br>257 dosed | 1.5 mg oral tivozanib once daily for 3 weeks followed by 1 week off study drug (1 cycle = 4 weeks [3 weeks on, 1 week off]). Cycles were repeated every 4 weeks.<br><br>400 mg sorafenib twice daily for 4 weeks (1 cycle) | Completed<br>Jul 2013        | Trough serum concentration measurements suggest that tivozanib had reached steady-state concentrations by 14 days after the first dose. Observations obtained during and after a 7-day rest showed a slow decrease in serum concentration, consistent with a terminal $t_{1/2}$ that is substantially longer than the dosing interval. Results are consistent with previously observed PK data for tivozanib trough concentrations with daily dosing. |
| AV-951-15-303 | Phase 3, randomized, controlled, multicenter, open-label study to compare tivozanib to sorafenib in subjects with refractory advanced RCC | Adult subjects with histologically or cytologically confirmed RCC with a clear cell component, ECOG PS of 0 or 1 and life expectancy $\geq 3$ months | Evaluate drug serum levels of tivozanib and sorafenib vs. clinical activity | 350 enrolled<br>343 dosed<br>Tivozanib 175 enrolled<br>173 dosed<br>Sorafenib 175 enrolled<br>170 dosed | 1.5 mg oral tivozanib once daily for 3 weeks followed by 1 week off study drug (1 cycle = 4 weeks [3 weeks on, 1 week off]). Cycles were repeated every 4 weeks.<br><br>400 mg sorafenib twice daily for 4 weeks (1 cycle) | Ongoing (survival follow-up) | The PK measurements obtained in this study were peak levels for CID1 and trough levels for CID15 and did not allow for standard PK analysis; therefore, only standard statistical summaries of concentration by nominal sampling day were calculated. Overall, the mean tivozanib CID15 concentration was consistent with prior experience with tivozanib.                                                                                            |

Source: Summary of Clinical Pharmacology Studies Table 19 (Section 2.7.2)

Note: 1.5 mg and 1 mg in this table are in the form of tivozanib hydrochloride, which is equivalent to 1.34 mg and 0.89 mg tivozanib free base.

A summary of results for PK parameters is provided in Table 3 below.

| Study ID                   | Type of Study      | No/ Gender (F/M) | Regimen                        | Cycle | Day                         | Doses (mg)       | PK Parameters<br>Arithmetic Mean $\pm$ STD (%CV) |                                    |                                           |                                    |                                     |                                     |                                    |
|----------------------------|--------------------|------------------|--------------------------------|-------|-----------------------------|------------------|--------------------------------------------------|------------------------------------|-------------------------------------------|------------------------------------|-------------------------------------|-------------------------------------|------------------------------------|
|                            |                    |                  |                                |       |                             |                  | $T_{max}$ or $T_{max,55}$ (hr) <sup>a</sup>      | $C_{max}$ or $C_{max,55}$ (ng/mL)  | $AUC_{0-24hr}$ or $AUC_{0-55}$ (ng·hr/mL) | $AUC_{0-24}$ (ng·hr/mL)            | $t_{1/2}$ (hr)                      | CL/F (mL/hr)                        | $V_z/F$ (L)                        |
| AV-951-10-111              | Mass Balance       | 0/8              | SD                             |       |                             | 1.5 <sup>b</sup> | 10.0<br>(3.00, 24.0)                             | 12.1 $\pm$ 5.67<br>(46.9)          | NC                                        | 1084 $\pm$ 417<br>(38.4)           | 89.3 $\pm$ 23.5<br>(26.3)           | 1450 $\pm$ 652<br>(45.1)            | NC                                 |
| AV-951-10-112 <sup>c</sup> | QTc                | 33/17            | QD 21 Days                     |       |                             | 1.5              | NA                                               | NA                                 | NA                                        | NA                                 | NA                                  | NA                                  | NA                                 |
| AV-951-10-115              | Food Effect        | 11/19            | SD Fed                         |       |                             | 1.5              | 24.0<br>(5.00, 48.0)                             | 14.4 $\pm$ 3.11<br>(21.6)          | NC                                        | 2491 $\pm$ 764<br>(30.7)           | 122 $\pm$ 31.1<br>(25.5)            | 593 $\pm$ 201<br>(33.9)             | 98.8 $\pm$ 23.0<br>(23.3)          |
|                            |                    |                  | SD Fasted                      |       |                             | 1.5              | 3.0<br>(3.00, 96.0)                              | 18.8 $\pm$ 5.50<br>(29.3)          | NC                                        | 2309 $\pm$ 745<br>(32.3)           | 121 $\pm$ 29.9<br>(24.7)            | 640 $\pm$ 206<br>(32.2)             | 107 $\pm$ 28.4<br>(26.5)           |
| AV-951-11-116              | DDI Keto           | 11/15            | SD Tivo                        |       |                             | 1.5              | 10.0<br>(3.00, 18.0)                             | 20.2 $\pm$ 8.55<br>(42.3)          | NC                                        | 2223 $\pm$ 903<br>(40.6)           | 117 $\pm$ 40.1<br>(34.3)            | 698 $\pm$ 282<br>(40.4)             | 108 $\pm$ 29.4<br>(27.2)           |
|                            |                    |                  | SD Tivo+ Steady-state Keto     |       |                             | 1.5              | 7.53<br>(3.00, 24.0)                             | 20.0 $\pm$ 6.76<br>(33.8)          | NC                                        | 2491 $\pm$ 1115<br>(44.8)          | 112 $\pm$ 39.5<br>(35.3)            | 621 $\pm$ 219<br>(35.3)             | 93.8 $\pm$ 30.5<br>(32.5)          |
| AV-951-11-117              | DDI Rifampin       | 9/21             | SD Tivo                        |       |                             | 1.5              | 10.0<br>(3.00, 24.0)                             | 25.2 $\pm$ 6.39<br>(25.4)          | NC                                        | 2398 $\pm$ 777<br>(32.4)           | 121 $\pm$ 39.8<br>(32.9)            | 606 $\pm$ 169<br>(27.9)             | 105 $\pm$ 46.7<br>(44.5)           |
|                            |                    |                  | SD Tivo+ Steady-state Rifampin |       |                             | 1.5              | 3.00<br>(3.00, 10.0)                             | 27.5 $\pm$ 8.31<br>(30.2)          | NC                                        | 1127 $\pm$ 201<br>(17.8)           | 54.0 $\pm$ 16.7<br>(30.9)           | 1220 $\pm$ 206<br>(16.9)            | 94.5 $\pm$ 32.7<br>(34.6)          |
| AV-951-12-118              | Hepatic impairment | 14/30            | SD Tivo                        |       |                             | 1.5              | Normal<br>3.0 (3.0, 96.0)                        | Normal<br>15.90 $\pm$ 4.57<br>Mild | NC                                        | Normal<br>1680 $\pm$ 598.8<br>Mild | Normal<br>103.0 $\pm$ 27.51<br>Mild | Normal<br>902.8 $\pm$ 328.6<br>Mild | Normal<br>124.3 $\pm$ 22.6<br>Mild |
|                            |                    |                  |                                |       | Moderate<br>3.0 (3.0, 36.0) |                  | Moderate<br>16.21 $\pm$ 3.69                     | Moderate<br>1960 $\pm$ 1121        |                                           | Moderate<br>118.7 $\pm$ 42.24      | Moderate<br>849.3 $\pm$ 380.8       | Moderate<br>127.2 $\pm$ 24.7        |                                    |
|                            |                    |                  |                                |       | Severe<br>4.0 (3.0, 48.0)   |                  | Severe<br>21.66 $\pm$ 9.17                       | Severe<br>4449 $\pm$ 2946          |                                           | Severe<br>316.2 $\pm$ 205.8        | Severe<br>488.3 $\pm$ 359.1         | Severe<br>153.2 $\pm$ 46.9          |                                    |
|                            |                    |                  |                                |       | Severe<br>3.0 (3.0, 48.0)   |                  | Severe<br>17.33 $\pm$ 4.66                       | Severe<br>6715 $\pm$ 5519          |                                           | Severe<br>577.8 $\pm$ 592.5        | Severe<br>302.5 $\pm$ 176.3         | Severe<br>159.2 $\pm$ 27.3          |                                    |
| AV-951-09-109              | BioEq              | 8/26             | SD Tablet                      |       |                             | 1.5              | 10.0<br>(3.00, 48.0)                             | 19.3 $\pm$ 5.32<br>(27.6)          | NC                                        | 2030 $\pm$ 524<br>(25.8)           | 123 $\pm$ 54.5<br>(44.3)            | NC                                  | NC                                 |
|                            |                    |                  | SD Capsule                     |       |                             | 1.5              | 10.0<br>(3.00, 24.0)                             | 18.2 $\pm$ 5.75<br>(31.6)          | NC                                        | 1950 $\pm$ 500<br>(25.7)           | 108 $\pm$ 34.8<br>(32.1)            | NC                                  | NC                                 |

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| AV-951-03-B01              | FIH           | 14/27                       | QD x 28d, 14d off | 1     | 1   | 1          | 6.015                                                     | 9.293±                                          | 131.2±52.6*                                             | NRI                           | NRI                   | NRI          | NC       |               |    |         |      |    |    |    |    |    |              |         |    |     |     |    |
|----------------------------|---------------|-----------------------------|-------------------|-------|-----|------------|-----------------------------------------------------------|-------------------------------------------------|---------------------------------------------------------|-------------------------------|-----------------------|--------------|----------|---------------|----|---------|------|----|----|----|----|----|--------------|---------|----|-----|-----|----|
|                            |               |                             |                   |       |     |            | (1.00, 24.03)                                             | 6.386 (68.7)                                    | (40.1)                                                  |                               |                       |              |          |               |    |         |      |    |    |    |    |    |              |         |    |     |     |    |
|                            |               |                             |                   |       |     |            | 1.5                                                       | 6.00                                            | 10.19±                                                  |                               |                       |              |          | 159.2±69.4*   | NC | NC      | NC   | NC |    |    |    |    |              |         |    |     |     |    |
|                            |               |                             |                   |       |     |            | (1.00, 24.0)                                              | 4.934 (48.4)                                    | (43.6)                                                  |                               |                       |              |          |               |    |         |      |    |    |    |    |    |              |         |    |     |     |    |
|                            |               |                             |                   |       |     |            | 2                                                         | 24.00                                           | 17.65±                                                  |                               |                       |              |          | 274.3±83.6*   |    |         |      |    | NC | NC | NC | NC |              |         |    |     |     |    |
|                            |               |                             |                   |       |     |            | (2.02, 24.0)                                              | 6.861 (38.9)                                    | (30.5)                                                  |                               |                       |              |          |               |    |         |      |    |    |    |    |    |              |         |    |     |     |    |
|                            |               |                             |                   |       |     |            | 1                                                         | 28                                              | 1                                                       |                               |                       |              |          | 4.010         |    |         |      |    |    |    |    |    | 50.03±       | 856.0±  | NC | NRI | NRI | NC |
|                            |               |                             |                   |       |     |            |                                                           |                                                 |                                                         |                               |                       |              |          | (0.38, 24.00) |    |         |      |    |    |    |    |    | 21.17 (42.3) | 396.6*  |    |     |     |    |
|                            |               |                             |                   |       |     |            |                                                           |                                                 |                                                         |                               |                       |              |          | 1.5           |    |         |      |    |    |    |    |    | 2.000        | 67.46 ± |    |     |     |    |
| (0.50, 24.00)              | 45.55 (67.5)  | (46.3)                      | 813.4*            |       |     |            |                                                           |                                                 |                                                         |                               |                       |              |          |               |    |         |      |    |    |    |    |    |              |         |    |     |     |    |
| 2                          | 24.00         | 110.0 ±                     | 1997.2±           | NC    | NC  | NRI        | NC                                                        |                                                 |                                                         |                               |                       |              |          |               |    |         |      |    |    |    |    |    |              |         |    |     |     |    |
| (2.00, 24.08)              | 61.43 (55.8)  | 1054.6*                     |                   |       |     |            |                                                           |                                                 |                                                         |                               |                       |              |          |               |    |         |      |    |    |    |    |    |              |         |    |     |     |    |
| 2                          | 1             | 1                           | 4.000             |       |     |            |                                                           | 14.40 ±                                         | 245.4±                                                  | NRI                           | NRI                   | NRI          | NC       |               |    |         |      |    |    |    |    |    |              |         |    |     |     |    |
|                            |               |                             | (0.50, 24.00)     |       |     |            |                                                           | 8.090 (56.2)                                    | 116.4*                                                  |                               |                       |              |          |               |    |         |      |    |    |    |    |    |              |         |    |     |     |    |
|                            |               |                             | 1.5               |       |     |            |                                                           | 23.970                                          | 13.35 ±                                                 |                               |                       |              |          | 236.6±        |    |         |      |    |    |    |    |    |              |         |    |     |     |    |
| (1.00, 24.05)              | 5.355 (40.1)  | (42.5)                      | 100.5*            |       |     |            |                                                           |                                                 |                                                         |                               |                       |              |          |               |    |         |      |    |    |    |    |    |              |         |    |     |     |    |
| 2                          | 4.000         | 24.97 ±                     | 400.2±            |       |     |            |                                                           | NC                                              | NC                                                      |                               |                       |              |          | NC            | NC |         |      |    |    |    |    |    |              |         |    |     |     |    |
| (2.07, 24.00)              | 15.03 (60.2)  | 244.4*                      |                   |       |     |            |                                                           |                                                 |                                                         |                               |                       |              |          |               |    |         |      |    |    |    |    |    |              |         |    |     |     |    |
|                            |               | (61.1)                      | 244.4*            |       |     |            |                                                           |                                                 |                                                         |                               |                       |              |          |               |    |         |      |    |    |    |    |    |              |         |    |     |     |    |
| AV-951-08-105 <sup>d</sup> | NSCLC         | 13/4                        | QD continuous     | 1     |     |            | Trough                                                    |                                                 |                                                         |                               |                       |              |          |               |    | Samples | Only |    |    |    |    |    |              |         |    |     |     |    |
|                            |               |                             |                   | 1.5   |     |            | Trough                                                    |                                                 |                                                         |                               |                       |              |          |               |    | Samples | Only |    |    |    |    |    |              |         |    |     |     |    |
| AV-951-07-201              | Ph2 Mono RCC  | 7/14                        | QD x 28d; 7d off  | 1     | 1   | 1.5        | 4.000                                                     |                                                 |                                                         | 15.51 ±                       | 258.2 ± 197.0         | NC           | NC       |               |    | NC      | NC   |    |    |    |    |    |              |         |    |     |     |    |
|                            |               |                             |                   |       |     |            | (2.00, 23.95)                                             |                                                 |                                                         | 11.70 (75.4)                  | (76.3)                |              |          |               |    |         |      |    |    |    |    |    |              |         |    |     |     |    |
|                            |               |                             |                   | 1     | 21  | 1.5        | 2.00                                                      |                                                 |                                                         | 94.29 ±                       | 1640.6 ±              | NC           | NRI      |               |    | NRI     | NC   |    |    |    |    |    |              |         |    |     |     |    |
|                            |               |                             |                   |       |     |            | (0.00, 24.17)                                             |                                                 |                                                         | 37.80 (40.1)                  | 644.9 (39.3)          |              |          |               |    |         |      |    |    |    |    |    |              |         |    |     |     |    |
| Study ID                   | Type of Study | No/ Gender (F/M)            | Regimen           | Cycle | Day | Doses (mg) | PK Parameters                                             |                                                 |                                                         |                               |                       |              |          |               |    |         |      |    |    |    |    |    |              |         |    |     |     |    |
|                            |               |                             |                   |       |     |            | T <sub>max</sub> or T <sub>max,ss</sub> (hr) <sup>a</sup> | C <sub>max</sub> or C <sub>max,ss</sub> (ng/mL) | AUC <sub>0-24hr</sub> or AUC <sub>0,ss</sub> (ng·hr/mL) | AUC <sub>0-∞</sub> (ng·hr/mL) | t <sub>1/2</sub> (hr) | CL/F (mL/hr) | Vz/F (L) |               |    |         |      |    |    |    |    |    |              |         |    |     |     |    |
| AV-951-10-202              | Ph2 Mono RCC  | 24/81                       | QD x 28d; 7d off  | 2     | 1   | 1.5        |                                                           |                                                 | Trough                                                  | Samples                       | Only                  |              |          |               |    |         |      |    |    |    |    |    |              |         |    |     |     |    |
| AV-951-09-301 <sup>d</sup> | Ph3 Mono RCC  | 75/184 (Tivozanib arm only) | QD x 28d; 7d off  | 1     | 21  | 1.5        |                                                           |                                                 | Trough                                                  | Samples                       | Only                  |              |          |               |    |         |      |    |    |    |    |    |              |         |    |     |     |    |
| AV-951-15-303              | Ph 3 Mono RCC | 49/126 (Tivozanib arm only) | QD x 28d; 7d off  | 1     | 1   | 1.5        |                                                           | 12.10 ±                                         | 6.437 (53.2)                                            |                               |                       |              |          |               |    |         |      |    |    |    |    |    |              |         |    |     |     |    |

<sup>a</sup> Median (min, max) is presented for T<sub>max</sub>, rather than arithmetic mean.  
<sup>b</sup> [<sup>14</sup>C]-tivozanib.  
<sup>c</sup> Only evaluated PK/PD relationship  
<sup>d</sup> Only C<sub>trough</sub> available  
<sup>e</sup> AUC<sub>0,ss</sub> for Study AV-951-03-B01  
 AUC<sub>0-24hr</sub> = area under the concentration- time curve from zero to 24 hours; AUC<sub>0,ss</sub> = area under the concentration-time curve during a dosing interval at steady-state; AUC<sub>0-∞</sub> = area under the concentration-time curve from zero to infinity; BioEq = bioequivalence; CL/F = apparent oral clearance; C<sub>max</sub> = maximum concentration; C<sub>max,ss</sub> = maximum concentration at steady state; d/D = day; DDI = drug-drug interaction; F = female; FIH = first-in-human; ID = identification; Keto → ketoconazole; M = male; NA = not applicable; NC = not calculated; NRI = not reported here within as values are inaccurate due to limited sampling scheme; NSCLC = non-small cell lung cancer; Ph = phase; Q = every; RCC = renal cell carcinoma; SD = single dose; t<sub>1/2</sub> = terminal elimination half-life; T<sub>max</sub> = time to maximum concentration; T<sub>max,ss</sub> = time to maximum concentration at steady state; Vz/F = apparent oral volume of distribution.

Source: Summary of Clinical Pharmacology Studies Table 20 (Section 2.7.2)

Note: 1.5 mg and 1 mg in this table are in the form of tivozanib hydrochloride, which is equivalent to 1.34 mg and 0.89 mg tivozanib free base.

Note that the C<sub>max</sub> and AUC provided in above table were arithmetic parameters, the geometric mean and CV% for C<sub>max</sub> and AUC<sub>0-24</sub> at steady state in patients with RCC (study AV-951-07-201) were 86.9 (66%) ng/mL and 1510 (67%) ng·h/mL.

### Effect of Renal Impairment

No dose adjustment is recommended for patients with renal impairment (creatinine clearance [CLcr] 15-89 mL/min, estimated by Cockcroft-Gault). The basis for this recommendation is listed as follows:

- 1) The lack of relationship between tivozanib clearance and creatinine clearance. In the PopPK analysis, renal impairment, as quantified by creatinine clearance (CLcr) with median 76.2 mL/min and range from 26.8 to 210 mL/min, did not have a statistically significant effect on the PK of tivozanib.
- 2) A small fraction (11.8%) of the administered tivozanib was excreted in urine.
- 3) The lack of renal function relation AE observed in the clinical trials, including 2 patients with severe renal impairment. The Incidence rate of acute renal failure is low (Grade1-5, 5.2%, grade3-4, 2.3%) in the pivotal study; no increased safety signals were observed when the AE profile for the 2 patients with severe renal impairment were analyzed, and they were both on therapy for about 1.3 years, indicating tivozanib was well tolerated. Renal and urinary disorders data is summarized in table 4 below.

Given that a higher proportion of patients within the proposed indication, refractory/relapsed renal cell carcinoma, may have severe renal impairment compared to the general population, who can potentially benefit from tivozanib treatment, no dose adjustment is recommended for patients with renal impairment (creatinine clearance [CLcr] 15-89 mL/min, estimated by Cockcroft-Gault).

Table 4. Renal and urinary disorders

| System Organ Class Preferred Term                                                                          | AV-951-15-303          |                        | AV-951-09-301          |                        | AV-951-09-902          | Other                  | Total Tivozanib (n=1008) n(%) |
|------------------------------------------------------------------------------------------------------------|------------------------|------------------------|------------------------|------------------------|------------------------|------------------------|-------------------------------|
|                                                                                                            | Tivozanib (n=173) n(%) | Sorafenib (n=170) n(%) | Tivozanib (n=259) n(%) | Sorafenib (n=257) n(%) | Tivozanib (n=161) n(%) | Tivozanib (n=415) n(%) |                               |
| <b>TEAEs</b> (Source: Summary of Safety, section 2.7.4, table 4)                                           |                        |                        |                        |                        |                        |                        |                               |
| <b>Renal and urinary disorders</b>                                                                         | <b>37 (21.4)</b>       | <b>22 (12.9)</b>       | <b>34 (13.1)</b>       | <b>25 (9.7)</b>        | <b>10 (6.2)</b>        | <b>51 (12.3)</b>       | <b>132 (13.1)</b>             |
| Hematuria                                                                                                  | 8 (4.6)                | 3 (1.8)                | 4 (1.5)                | 0                      | 0                      | 8 (1.9)                | 20 (2.0)                      |
| Proteinuria                                                                                                | 16 (9.2)               | 7 (4.1)                | 24 (9.3)               | 21 (8.2)               | 5 (3.1)                | 34 (8.2)               | 79 (7.8)                      |
| <b>TEADRs</b> (Source: Summary of Safety, section 2.7.4, table 6)                                          |                        |                        |                        |                        |                        |                        |                               |
| <b>Renal and urinary disorders</b>                                                                         | <b>13 (7.5)</b>        | <b>8 (4.7)</b>         | <b>16 (6.2)</b>        | <b>8 (3.1)</b>         | <b>1 (0.6)</b>         | <b>20 (4.8)</b>        | <b>50 (5.0)</b>               |
| Proteinuria                                                                                                | 11 (6.4)               | 5 (2.9)                | 14 (5.4)               | 6 (2.3)                | 1 (0.6)                | 19 (4.6)               | 45 (4.5)                      |
| <b>TEAEs Leading to Discontinuation of Study Drug</b> (Source: Summary of Safety, section 2.7.4, table 13) |                        |                        |                        |                        |                        |                        |                               |

|                                                                                                             |                |                |                |          |          |                |                |
|-------------------------------------------------------------------------------------------------------------|----------------|----------------|----------------|----------|----------|----------------|----------------|
| <b>Renal and urinary disorders</b>                                                                          | <b>2 (1.2)</b> | <b>2 (1.2)</b> | <b>2 (0.8)</b> | <b>0</b> | <b>0</b> | <b>5 (1.2)</b> | <b>9 (0.9)</b> |
| <b>TEADRs Leading to Discontinuation of Study Drug</b> (Source: Summary of Safety, section 2.7.4, table 14) |                |                |                |          |          |                |                |
| <b>Renal and urinary disorders</b>                                                                          | <b>1 (0.6)</b> | <b>1 (0.6)</b> | <b>0</b>       | <b>0</b> | <b>0</b> | <b>4 (1.0)</b> | <b>5 (0.5)</b> |

### Effect of Hepatic Impairment

The effect of hepatic impairment on the PK of tivozanib was assessed in a dedicated hepatic impairment study and by population PK analysis.

In the dedicated study, the patients were originally classified according to Child-Pugh Scores, there were 8 patients with mild hepatic impairment (Child-Pugh A), 8 patients with moderate hepatic impairment (Child-Pugh B) and 6 patients with severe hepatic impairment (Child-Pugh C). Results showed that the exposure to tivozanib in patients with mild hepatic impairment was similar to that in patients with normal hepatic function (GMR of  $AUC_{0-\infty}$ : 1.1 ). However, tivozanib was eliminated more slowly in patients with moderate or severe hepatic impairment. The mean tivozanib exposure ( $AUC_{0-\infty}$ ) increased 2.2-fold in patients with moderate (Child-Pugh B) hepatic impairment and 3.4-fold in patients with severe (Child-Pugh C) hepatic impairment.

| Table 5. Geometric Mean Ratio (90% CI) relative to normal patients for tivozanib PK parameters |                          |                            |                            |                                |                                    |                                  |
|------------------------------------------------------------------------------------------------|--------------------------|----------------------------|----------------------------|--------------------------------|------------------------------------|----------------------------------|
| <b>Child-Pugh Category</b>                                                                     | <b>CL/F (L/h)</b>        | <b>V<sub>d</sub>/F (L)</b> | <b>t<sub>1/2</sub> (h)</b> | <b>C<sub>max</sub> (ng/mL)</b> | <b>AUC<sub>all</sub> (ng h/mL)</b> | <b>AUC<sub>∞</sub> (ng h/mL)</b> |
| Mild                                                                                           | 0.907<br>(0.628, 1.31)   | 1.02<br>(0.836, 1.24)      | 1.12<br>(0.802, 1.57)      | 1.04<br>(0.838, 1.28)          | 1.08<br>(0.818, 1.42)              | 1.1<br>(0.764, 1.59)             |
| Moderate                                                                                       | 0.448<br>(0.31, 0.646)*  | 1.16<br>(0.955, 1.41)      | 2.59<br>(1.86, 3.63)*      | 1.31<br>(1.06, 2.19)           | 1.66<br>(1.26, 2.19)*              | 2.23<br>(1.55, 3.23)*            |
| Severe                                                                                         | 0.297<br>(0.197, 0.447)* | 1.27<br>(1.02, 1.58)       | 4.27<br>(2.94, 6.21)*      | 1.1<br>(0.867, 1.39)           | 1.88<br>(1.38, 2.56)*              | 3.37<br>(2.24, 5.08)*            |

Source: Summary of Clinical Pharmacology Studies Table 29 (Section 2.7.2)

After re-classifying the patients in the dedicated study by NCI-ODWG criteria, there were 12 patients with mild hepatic impairment, 5 patients with moderate hepatic impairment, 0 patients with severe hepatic impairment. Mean tivozanib exposure ( $AUC_{0-\infty}$ ) increased 1.79-fold in patients with mild hepatic impairment and 3.49-fold in patients with moderate hepatic impairment. The effect of hepatic impairment on the clearance of tivozanib was larger when

patients were classified by NCI-ODWG criteria compared to Child-Pugh criteria in the dedicated study.

| NCI-ODWG Group: | Values are Presented as Geometric Mean Ratios (90% CI) Relative to Normal Hepatic Functioning Group |                            |                              |                      |                         |                      |
|-----------------|-----------------------------------------------------------------------------------------------------|----------------------------|------------------------------|----------------------|-------------------------|----------------------|
|                 | C <sub>max</sub> (ng/mL)                                                                            | AUC <sub>t</sub> (ng·h/mL) | AUC <sub>inf</sub> (ng·h/mL) | t <sub>1/2</sub> (h) | CL/F (L/h)              | Vd/F (L)             |
| Mild (N=12)     | 1.31<br>(1.1-1.55)                                                                                  | 1.44<br>(1.13-1.82)        | 1.79<br>(1.29-2.47)*         | 1.93<br>(1.4-2.65)*  | 0.56<br>(0.405-0.774)*  | 1.08<br>(0.913-1.27) |
| Moderate (N=5)  | 1.11<br>(0.871-1.41)                                                                                | 1.89<br>(1.35-2.64)*       | 3.49<br>(2.21-5.49)*         | 4.23<br>(2.71-6.61)* | 0.287<br>(0.182-0.452)* | 1.21<br>(0.96-1.53)  |
| Severe (N=0)    | -                                                                                                   | -                          | -                            | -                    | -                       | -                    |

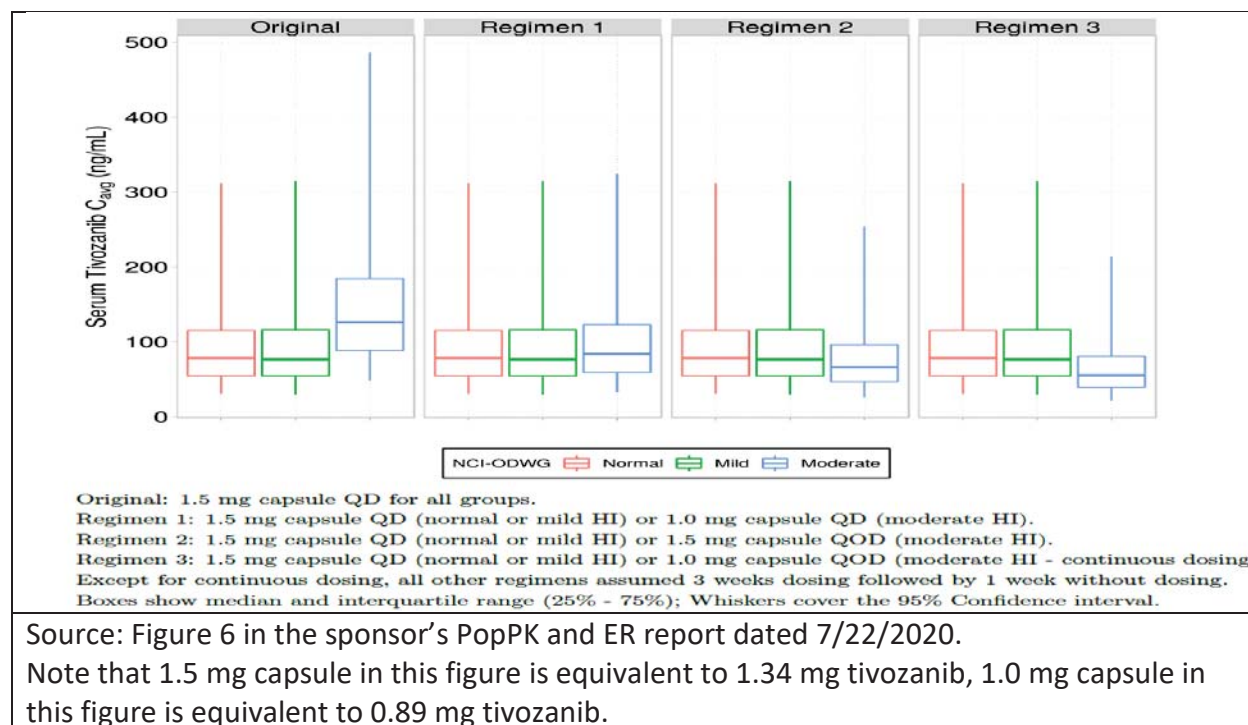
\*90% CI falls completely outside the normal equivalence range of 0.8-1.25

Source: Applicant's response to FDA clinical pharmacology IR received on 07/30/2020

Therefore, in the PopPK analysis, NCI-ODWG criteria was used to classify the patients, not only because that dosing recommendation based on NCI-ODWG criteria is more conservative, given the larger fold changes in AUC observed, but also that the majority of the patients were cancer patients. In the whole PopPK dataset, there were 570 patients with normal hepatic function, 83 patients with mild hepatic impairment, 10 patients with moderate hepatic impairment, 0 patients with severe hepatic impairment. The PopPK analysis indicated that mild hepatic impairment did not have an effect on the tivozanib CL/F, while patients with moderate hepatic impairment were found to have a 38.9% lower tivozanib CL/F compared to patients with normal hepatic function or mild hepatic impairment.

The PopPK analysis, using all data with more patients for both mild hepatic impairment and moderate hepatic impairment, provided a reliable estimate for the hepatic impairment effect, given disease status was not found to be a significant covariate. Therefore, simulations were conducted based on the PK metrics generated from PopPK analysis. Simulation results (figure 1 below) indicated that 0.89 mg once daily (QD) for 3 weeks on and 1 week off in patients with moderate hepatic impairment is estimated to result in tivozanib exposure comparable to that in patients with normal hepatic function treated with 1.34 mg QD tivozanib for 3 weeks on and 1 week off. Therefore, in the absence of safety issues in the clinical trials, 0.89 mg once daily (QD) for 3 weeks on and 1 week off is recommended for patients with moderate hepatic impairment.

Figure 1, Simulated Tivozanib C<sub>avg</sub> During Cycle 2 by Dosing Regimen



### 19.4.3 Pharmacometrics Review

#### Population pharmacokinetics and exposure response analyses

**Aim:** 1) Incorporate data from AV-951-15-303 into the previously developed PopPK model describing the serum concentration of tivozanib over time; 2) Evaluate the impact of covariates on the PK of tivozanib; 3) Establish ER models describing efficacy (change in tumor size, PFS) and incidence of adverse events (increased blood pressure, HFS) as a function of predicted tivozanib exposure; 4) Evaluate the impact of covariates on the ER of tivozanib.

**Data:** This population pharmacokinetic (PopPK) and exposure response (ER) analyses is based on tivozanib exposure and clinical efficacy and safety data obtained from seven clinical studies (See Table 36). A total of 4351 tivozanib plasma PK concentration samples obtained from 666 patients were included in the updated PopPK model. Patient characteristics are summarized in Table 35.

Table 35. Summary of Clinical Studies used in PopPK analyses.

NDA/BLA Multi-disciplinary Review and Evaluation {NDA 212904}  
 {FOTIVDA, tivozanib}

| Study ID      | Study Title                                                                                                                                                                      | Dose                                   | N <sub>Obs</sub> per Subject | Schedule Route of Administration                                                                                                                                                  |
|---------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------|------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| KRN951/03-B01 | An open-label, Non-Randomized Dose Escalation Study of AV-951 Administered Orally to Patients with Solid Tumors                                                                  | Tivozanib 1, 1.5, 2, or 10 mg QD       | Dense and sparse sampling    | Oral, once daily for 28 days followed by a 14-day rest period with no treatment                                                                                                   |
| AV-951-09-109 | A Phase 1, Open label, Single Center, Randomized, Two-period Crossover Bio-equivalence Study of Single Doses of AV-951 in Healthy Volunteers                                     | A: 1.5 mg tablet<br>B: 1.5 mg capsule  | Dense sampling               | Subjects randomly assigned to one of 2 sequences:<br>1: A → B 2: B → A<br>Treatment A: single oral dose of tivozanib tablet<br>Treatment B: single oral dose of tivozanib capsule |
| AV-951-12-118 | A Phase 1, open-label, Single Dose Study to Evaluate the Pharmacokinetics, Safety and Tolerability of Tivozanib in Subjects with Hepatic Impairment and Normal Hepatic Function. | 1.5 mg tablet                          | Dense sampling               | Oral, single dose                                                                                                                                                                 |
| AV-951-07-201 | A Phase 2, Placebo-Controlled, Randomized, Discontinuation Trial of Tivozanib (AV-951) in Patients with Renal Cell Carcinoma                                                     | Tivozanib 1.5 mg                       | 12                           | Oral, once daily for 21 days followed by a 7-day rest period with no treatment X 4 cycles                                                                                         |
| AV-951-10-202 | A Phase 2 and Biomarker Study of Tivozanib in Subjects With Advanced Renal Cell Carcinoma                                                                                        | Tivozanib 1.5 mg                       | 3                            | Oral, once daily for 21 days followed by a 7-day rest period with no treatment X 4 cycles                                                                                         |
| AV-951-09-301 | A Phase 3, Randomized, Controlled, Multi-Center, Open-Label Study to Compare Tivozanib (AV-951) to Sorafenib in Subjects With Advanced Renal Cell Carcinoma                      | Tivozanib: 1.5 mg<br>Sorafenib: 400 mg | 4                            | Tivozanib oral once daily for 21 days followed by 7 days off treatment x 4 cycles.<br>Sorafenib oral twice daily x 4 cycles                                                       |
| AV-951-15-303 | A Phase 3, Randomized, Controlled, Multi-Center, Open-Label Study to Compare Tivozanib Hydrochloride to Sorafenib in Subjects With Refractory Advanced Renal Cell Carcinoma      | Tivozanib: 1.5 mg<br>Sorafenib: 400 mg | 2                            | Tivozanib oral once daily for 3 weeks followed by 7 days off treatment x 4 cycles.<br>Sorafenib oral twice daily x 4 cycles                                                       |

Source: Table 1 in the PopPK and ER report dated 7/22/2020.

Table 36. Summary of Patient Characteristics.

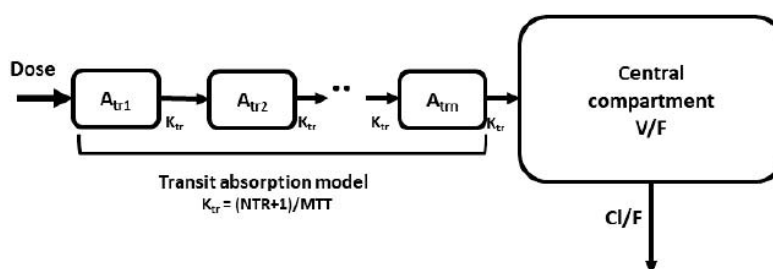
| Parameter               | All<br>(N=666)   | Parameter                        | All<br>(N=666)    |
|-------------------------|------------------|----------------------------------|-------------------|
| Dose (mg)               |                  | Creatinine ( $\mu\text{mol/L}$ ) |                   |
| 1                       | 20 (3.0%)        | Mean (SD)                        | 103 (27)          |
| 1.5                     | 638 (95.8%)      | Median (range)                   | 99 (40.2 - 212)   |
| 2                       | 7 (1.1%)         | Albumin (g/L)                    |                   |
| 10                      | 1 (0.2%)         | Mean (SD)                        | 41.1 (5.2)        |
| Gender                  |                  | Median (range)                   | 42 (20 - 86)      |
| Female                  | 188 (28.2%)      | ALT (U/L)                        |                   |
| Male                    | 478 (71.8%)      | Mean (SD)                        | 25.7 (22)         |
| Race                    |                  | Median (range)                   | 21 (4.5 - 312)    |
| Asian                   | 15 (2.3%)        | AST (U/L)                        |                   |
| Black                   | 19 (2.9%)        | Mean (SD)                        | 26.4 (21)         |
| Caucasian               | 621 (93.2%)      | Median (range)                   | 22 (-99 - 256)    |
| Unknown/Other           | 11 (1.7%)        | Bilirubin ( $\mu\text{mol/L}$ )  |                   |
| Age (yr)                |                  | Mean (SD)                        | 8.92 (8.4)        |
| Mean (SD)               | 57.9 (12)        | Median (range)                   | 7.75 (-99 - 56.4) |
| Median (range)          | 59 (18 - 88)     | Creatinine Clearance (mL/min)    |                   |
| Weight (kg)             |                  | Mean (SD)                        | 79.6 (28)         |
| Mean (SD)               | 79.9 (17)        | Median (range)                   | 76.2 (26.8 - 210) |
| Median (range)          | 78 (39 - 158)    | NCI-ODWG Classification          |                   |
| BMI ( $\text{kg/m}^2$ ) |                  | Normal                           | 570 (85.6%)       |
| Mean (SD)               | 27.4 (5.1)       | Mild                             | 83 (12.5%)        |
| Median (range)          | 26.8 (16 - 46.6) | Moderate                         | 10 (1.5%)         |
|                         |                  | Missing                          | 3 (0.5%)          |

Source: Table 2 in the PopPK and ER report dated 7/22/2020.

**Model:** The reference model was developed without the hepatic impairment study (AV-951-12-118) and consisted of a one-compartment structural pharmacokinetic (PK) model with a transit compartment absorption model (TCAM) and linear elimination. The structure of the model is shown in Figure 4. The model updated and re-evaluated with the dedicated hepatic impairment study (AV-951-12-118). Covariates that were evaluated include weight on V/F and sex, disease status, dose, creatinine clearance (CLcr), hepatic impairment on CL/F. Initially, hepatic impairment was included as a categorical covariate (normal versus mild or moderate impairment). Although the drop in OFV was significant ( $\Delta\text{OFV} -19$ ), the effect size of mild hepatic impairment was estimated to be approximately 0. The final model includes inter-individual variability (IIV) on all structural parameters, including mean transit time (MTT), apparent clearance (CL/F), and apparent central volume of distribution unadjusted for bioavailability (V/F) and covariates body weight effect on V/F and effects of sex and moderate hepatic impairment on CL/F. The parameter estimates of the final model are in Table 37. The final model was evaluated via Goodness of Fit and Visual Predictive Check plots (see

Figure 5 and Figure 6). The  $T_{1/2}$  of tivozanib was 129 hours and 110 hours in women and men, respectively. Typical CL/F was 0.651 L/h in women and 0.862 L/h in men. Volume of distribution was found to increase nearly proportionally with body weight. Typical value of volume distribution (95% CI) is 123 (121-126) L. Population PK modelling showed slightly high inter individual variability (82.5%, square root of estimated variability in %) in mean transit time (MTT) for absorption, likely due to enterohepatic recirculation of tivozanib, but moderate variability in distribution and elimination parameters (40.5% and 28.1% for CL/F and  $V_1/F$ , respectively).

Figure 4. Tivozanib Structural Model.



CL/F: Apparent clearance; V/F: Apparent volume of distribution; MTT: Mean transit time; NTR: Number of transit compartments;  $K_{tr}$ : Absorption transit rate;  $A_{trx}$ : Amount in transit compartment x.

Source: Figure 1 in the PopPK and ER report dated 7/22/2020.

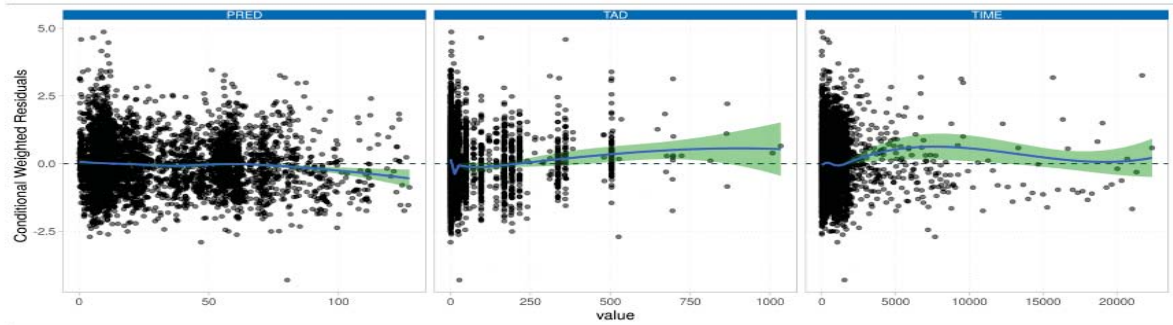
Table 37. Parameter Estimates of the Final Model.

| Parameter      | Description                        | Typical Value | RSE   | 95% CI             |
|----------------|------------------------------------|---------------|-------|--------------------|
| $\theta_1$     | NTR (fixed)                        | 0.537         | ..... |                    |
| $\theta_2$     | MTT (hr)                           | 1.20          | ..... | (1.13 - 1.27)      |
| $\theta_3$     | CL/F if Male ( $L \cdot h^{-1}$ )  | 0.815         | ..... | (0.778 - 0.853)    |
| $\theta_4$     | V/F (L)                            | 120.          | ..... | (116 - 125)        |
| $\theta_5$     | Proportional Scalar Female - CL/F  | -0.252        | 10.6  | (-0.304 - -0.2)    |
| $\theta_6$     | Allometric Exponent Weight - V/F   | 0.744         | 10.6  | (0.589 - 0.898)    |
| $\theta_7$     | Moderate ODWG on CL/F              | -0.389        | 11.7  | (-0.479 - -0.3)    |
| $\omega_{2.2}$ | IIV (MTT)                          | 0.681         | 13.8  | (0.496 - 0.865)    |
| $\omega_{3.3}$ | IIV (CL/F)                         | 0.164         | 6.9   | (0.142 - 0.186)    |
| $\omega_{4.3}$ | covar (CL/F, V/F)                  | 0.0707        | 11.8  | (0.0543 - 0.087)   |
| $\omega_{4.4}$ | IIV (V/F)                          | 0.0788        | 7.6   | (0.0672 - 0.0905)  |
| $\sigma_{1.1}$ | Proportional Residual Variance     | 0.117         | 2.1   | (0.112 - 0.122)    |
| $\sigma_{2.2}$ | Additive Residual Variance (ng/mL) | 0.0120        | 26.7  | (0.00574 - 0.0183) |

Note: RSE: Relative standard error; CI: Confidence interval; NTR: Number of transit compartments in the TCAM. MTT: Mean transit time through the TCAM. CL/F: Apparent systemic clearance.  $V_1/F$ : Apparent volume of distribution.  $\omega_X^2$ : Variance of the inter-individual variability of parameter X.  $\omega_{X,Y}^2$ : Covariance of the inter-individual variability of parameters X and Y.

Source: Table 10 in the PopPK and ER report 7/22/2020.

Figure 5. Goodness of Fit Plot.

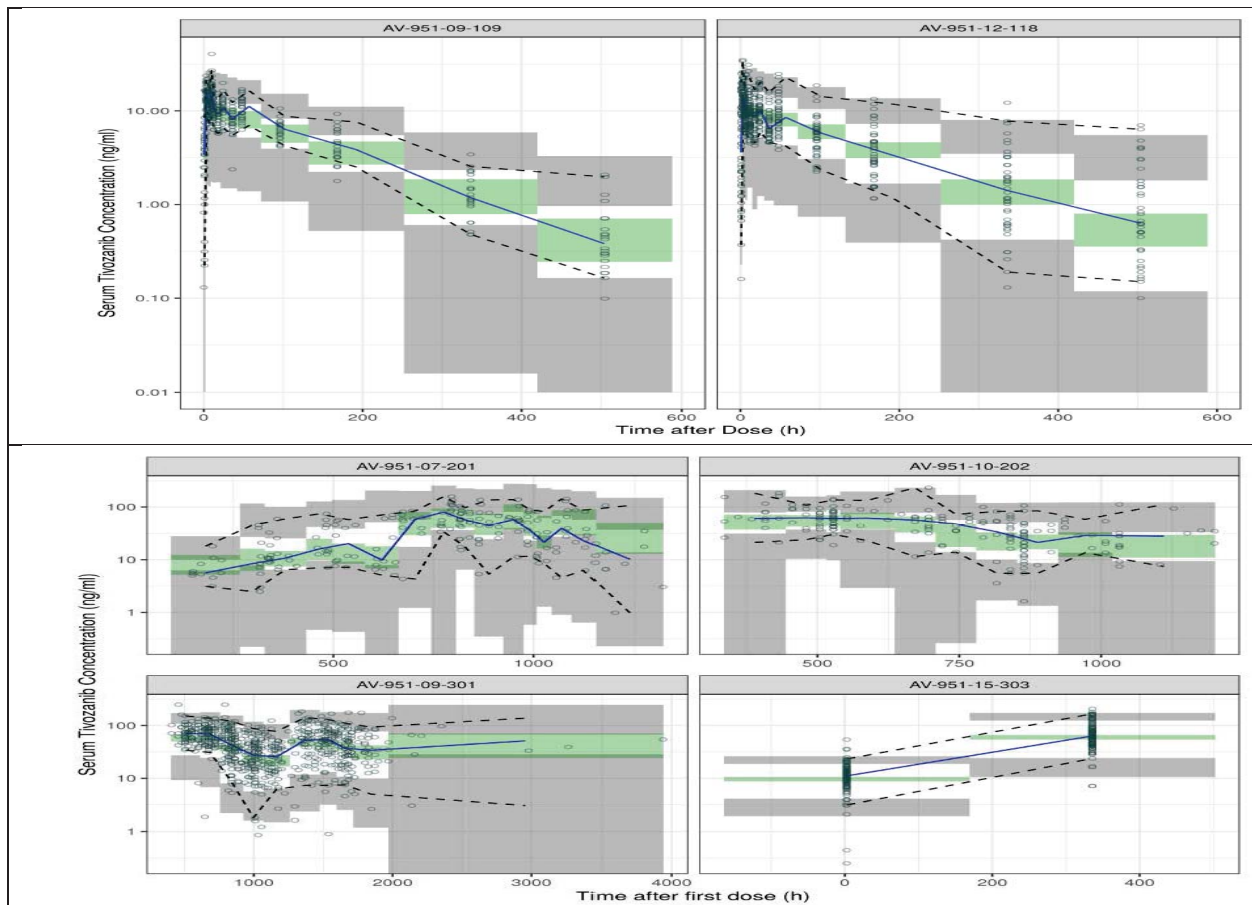


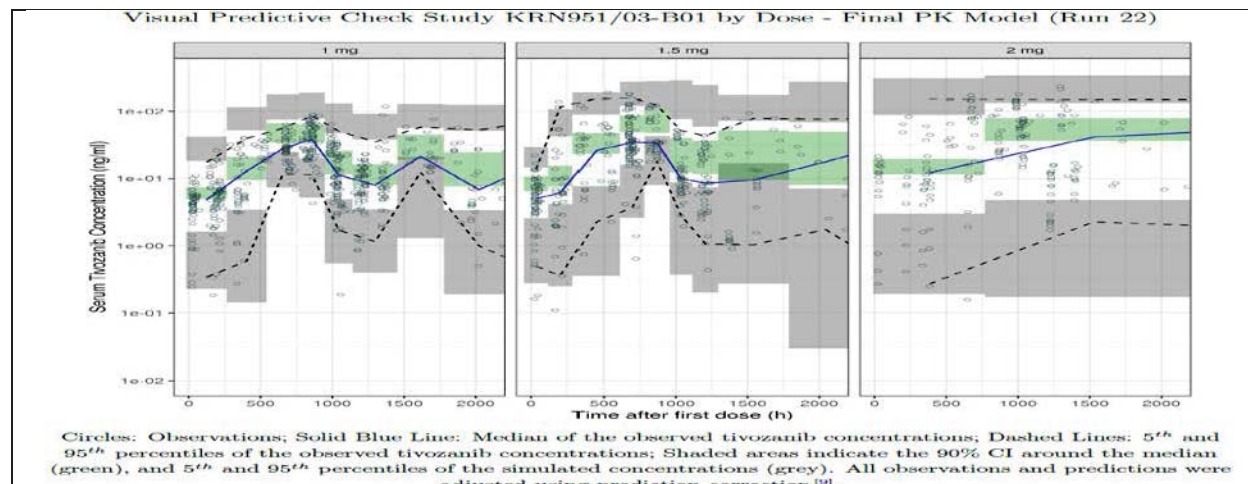
PRED: Population predicted serum tivozanib concentrations (ng/mL), TAD: Time after last dose (hr), TIME: Time after first dose (hr), Circles: Individual observations; Blue line and green shading: Loess smoothing line and 95% CI, Black dashed line: Line of identity.

Source: Figure A4 in the PopPK and ER report dated 7/22/2020.

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Figure 6. Predictive Corrected Visual Predictive Check Plot.





Source: Figure A4 in the PopPK and ER report dated 7/22/2020.

**Special Populations:** The PopPK analysis indicated that mild hepatic impairment did not have an impact on the tivozanib CL/F, while patients with moderate hepatic impairment were found to have a 38.9% lower tivozanib CL/F. To further check whether the PopPK analysis using all data can capture the feature of the 12 mild and 5 moderate HI patients in dedicated study with respect to CL/F, we summarized the empirical Bayesian estimates of CL/F by studies and HI categories by NCI as in Study. The popPK results for the HI study 118 are consistent with the non-compartment analysis results with respect to hepatic effect on PK. Mild patients in the study AV-951-12-118 (referred as 118) have lower CL than patients in other studies. In addition, the popPK analysis results using 118 study only are also consistent with 118 study using NCA. Overall, the PopPK results are sufficient to make conclusions on HI dosing recommendation.

Table 38. Summary of empirical Bayesian estimates of CL/F by studies and NCI HI categories.

| Study | NCI-ODWG | n  | PopPK GMR (90%CI)    | NCA GMR (90%CI)     |
|-------|----------|----|----------------------|---------------------|
| Other | Mild     | 71 | 1.028 (0.977, 1.080) | N/A                 |
| Other | Moderate | 5  | 1.067 (0.943, 1.208) | N/A                 |
| 118   | Mild     | 12 | 0.591 (0.492, 0.711) | 0.56 (0.405, 0.774) |
| 118   | Moderate | 5  | 0.373 (0.342, 0.406) | 0.287(0.182, 0.452) |

Source: Reviewer and adapted from Table 1 in the IR response dated 7/30/2020.

To assess hepatic impairment on tivozanib exposure and further support dose adjustment, four dosing regimens, based on either once daily (QD) or once every other day (QOD) dosing, were simulated using the final tivozanib popPK model:

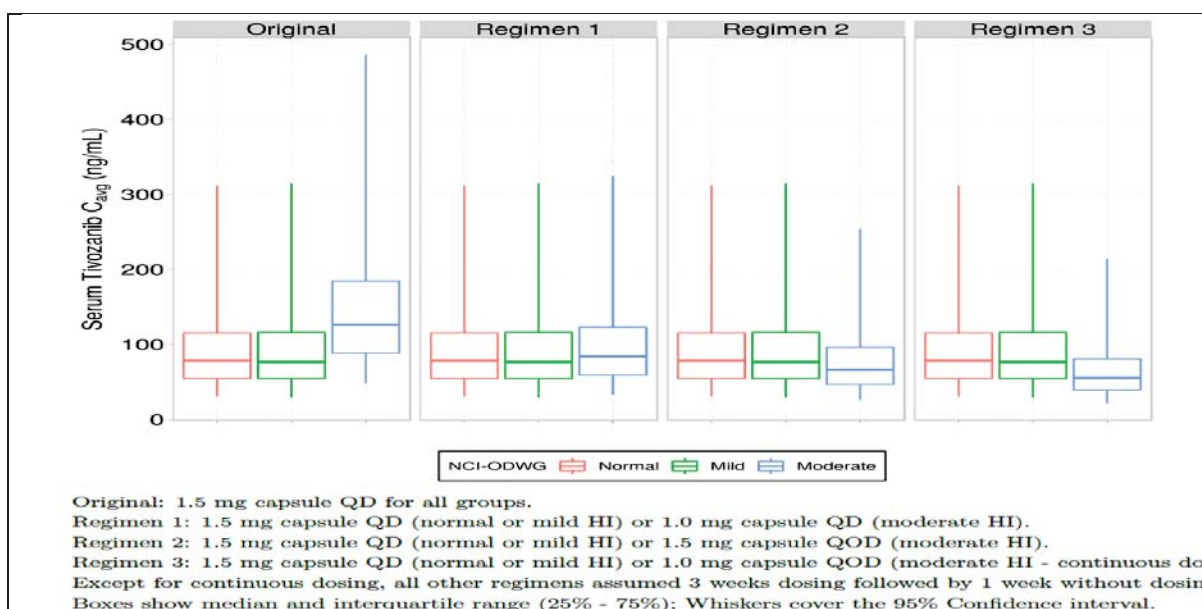
- Original: 1.5 mg capsule QD for all groups;
- Regimen 1: 1.5 mg capsule QD (normal or mild hepatic impairment) or 1.0 mg capsule QD (moderate hepatic impairment);
- Regimen 2: 1.5 mg capsule QD (normal or mild hepatic impairment) or 1.5 mg capsule QOD (moderate hepatic impairment);

- Regimen 3: 1.5 mg capsule QD (normal or mild hepatic impairment) or 1.0 mg capsule QOD (moderate hepatic impairment - continuous dosing).

Note that 1.5 mg capsule is equivalent to 1.34 mg tivozanib, 1.0 mg capsule in this figure is equivalent to 0.89 mg tivozanib.

For all dosing regimens, 2,000 virtual patient profiles per group were simulated and the average concentration ( $C_{avg}$ ) were summarized by dosing regimen. The simulation results are summarized in Figure 7. Simulated mean tivozanib exposure ( $AUC_{tau}$ ) increased 1.62-fold in patients with moderate hepatic impairment compared to patient with normal hepatic function or mild hepatic impairment. Simulation results indicated that 0.89 mg QD tivozanib (i.e., 1 mg capsule) for 3 weeks on and 1 week off in patients with moderate hepatic impairment can establish tivozanib exposure comparable to that in patients with normal hepatic function treated with 1.34 mg QD tivozanib for 3 weeks on and 1 week off. Therefore, in the absence of safety concerns, 0.89 mg once daily (QD) for 3 weeks on and 1 week off is recommended for patients with moderate hepatic impairment.

Figure 7. Simulated Tivozanib  $C_{avg}$  During Cycle 2 by Dosing Regimen.



| Regimen   | ODWG Class | Number of subjects | Mean   | SD     | Median | 95% CI   | IQR       |
|-----------|------------|--------------------|--------|--------|--------|----------|-----------|
| Original  | Normal     | 2000               | 101.00 | 89.10  | 78.50  | 30.7-311 | 54.7-113  |
|           | Mild       | 2000               | 102.00 | 103.00 | 76.50  | 29.4-315 | 54.7-116  |
|           | Moderate   | 2000               | 163.00 | 149.00 | 126.00 | 48.6-486 | 88.6-184  |
| Regimen 1 | Normal     | 2000               | 101.00 | 89.10  | 78.50  | 30.7-311 | 54.7-113  |
|           | Mild       | 2000               | 102.00 | 103.00 | 76.50  | 29.4-315 | 54.7-116  |
|           | Moderate   | 2000               | 109.00 | 99.00  | 84.00  | 32.4-324 | 59.1-123  |
| Regimen 2 | Normal     | 2000               | 101.00 | 89.10  | 78.50  | 30.7-311 | 54.7-113  |
|           | Mild       | 2000               | 102.00 | 103.00 | 76.50  | 29.4-315 | 54.7-116  |
|           | Moderate   | 2000               | 85.30  | 77.30  | 66.10  | 25.6-254 | 46.5-96.1 |
| Regimen 3 | Normal     | 2000               | 101.00 | 89.10  | 78.50  | 30.7-311 | 54.7-113  |
|           | Mild       | 2000               | 102.00 | 103.00 | 76.50  | 29.4-315 | 54.7-116  |
|           | Moderate   | 2000               | 71.40  | 64.60  | 55.30  | 21.5-214 | 39.1-80.1 |

SD: standard deviation; CI: confidence interval; IQR: Inter-quartile range.

Source: Figure 6 in the PopPK and ER report dated 7/22/2020.

Renal impairment, as quantified by creatinine clearance (CLcr) with median 76.2 mL/min and range from 26.8 to 210 mL/min, did not have a statistically significant effect on the PK of tivozanib. Therefore, no dose adjustments are required for patients with mild or moderate renal impairment. It is the general expectation that V/F scales linearly with WT. In addition, females were found to have a statistically significant, 25.2% lower CL/F compared to males.

**Exposure Response Analyses:** Cavg over a four-week treatment period was identified as the best predictor for efficacy compared to other exposure metrics. Cavg in cycle 2 was derived based on individual post-hoc PK parameter estimates from the final PK model. The efficacy endpoints of interest include tumor size and progression free survival (PFS) and the safety endpoint of interest include hand and foot syndrome (HFS) and blood pressure. All ER analyses were performed on data obtained in patients treated with either tivozanib or sorafenib in studies AV-951-09-301 and AV-951-15-303. Only for HFS, data obtained in study AV-951-07-201 was included from patients with exposure metrics.

**Exposure Efficacy Response Analyses:**

**Tumor Size:** A tumor growth inhibition model was developed to describe the change in tumor size as a function of time, tivozanib exposure, and covariates. Covariates including Cavg, study population (AV-951-09-301 vs. AV-951-15-303), baseline ECOG, sex, prior therapy, and International metastatic renal cell carcinoma database Consortium (IMDC) status were tested via the stepwise covariate modeling (SCM). Effects of Cavg on tumor shrinkage rate (KD), study population on tumor growth rate (KL), and ECOG status on baseline tumor size was identified as the best model describing change in tumor size as a function of time and tivozanib exposure. The model structure is shown in the equation below. The final model parameter estimates are summarized in Table 39. The model was further assessed via goodness of fit and predictive check plots (

Figure 8).

$$\begin{aligned} \frac{dA}{dt} &= K_L \cdot A - K_D \cdot e^{-\lambda \cdot t} \cdot A \\ K_{D_i} &= \hat{K}_D \cdot (1 + C_{\text{avg}K_D} \cdot (C_{\text{avg}} - 54.53)) \\ K_{L_i} &= \hat{K}_L \cdot (1 + \text{Refractory}_{K_L}) \\ A(t=0)_i &= A(\hat{t}=0) \cdot (1 + \text{ECOG}0_{A(t=0)}) \end{aligned}$$

Where A represents tumor size at time t.  $\hat{K}_L$  represents population tumor growth rate and  $\text{Refractory}_{K_L}$  represents the proportional change from  $\hat{K}_L$  for advanced refractory RCC patients. Similarly,  $\hat{K}_D$  represents population tumor shrinkage rate at median  $C_{\text{avg}}$ , with proportional change of  $C_{\text{avg}K_D}$  for each unit deviation in  $C_{\text{avg}}$ .  $A(\hat{t}=0)$  is population baseline tumor size if ECOG=1, and  $\text{ECOG}0_{A(t=0)}$  represents proportional change in baseline tumor size if ECOG=0.

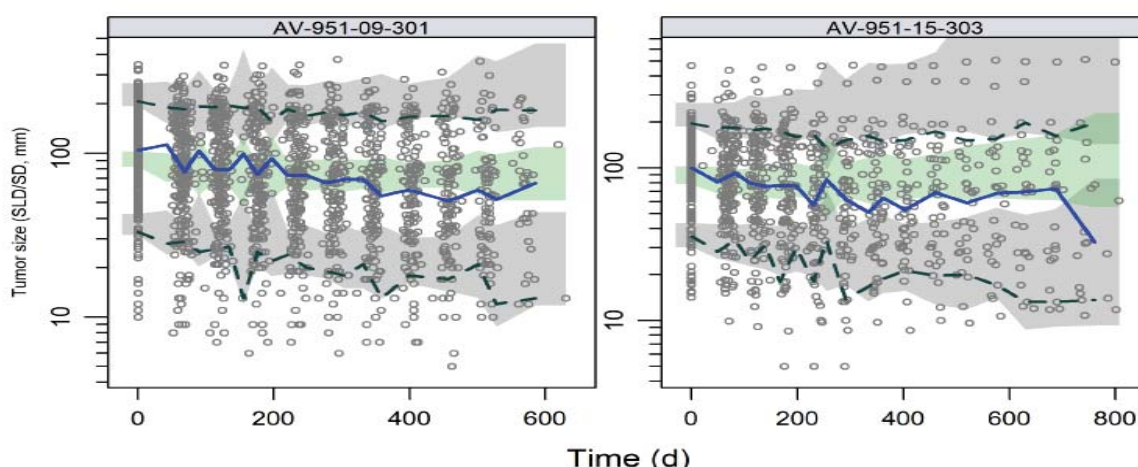
Table 39. Parameter Estimates of Final Tivozanib Tumor Size Model.

| Parameter                 | Estimate | RSE (%) | 95% CI               |
|---------------------------|----------|---------|----------------------|
| $\hat{K}_L$ (1/d)         | 0.000187 | 2       | (0.00018 - 0.000195) |
| $\text{Refractory}_{K_L}$ | 1.53     | 24.3    | (0.802 - 2.26)       |
| $\hat{K}_D$ (1/d)         | 0.00285  | 8.6     | (0.00237 - 0.00333)  |
| $C_{\text{avg}K_D}$       | 0.0128   | 24.1    | (0.00677 - 0.0189)   |
| $\lambda$ (1/d)           | 0.0146   | 13.2    | (0.0108 - 0.0184)    |
| $A(\hat{t}=0)$ (mm)       | 104.     | 5.4     | (92.6 - 114)         |
| $\text{ECOG}0_{A(t=0)}$   | -0.235   | 22.4    | (-0.339 - -0.132)    |
| Additive error (mm)       | 2.74     | 1.2     | (2.67 - 2.8)         |
| Proportional error        | 0.0763   | 0.7     | (0.0752 - 0.0773)    |
| $\omega_{K_L}^2$          | 1.61     | 11.7    | (1.24 - 1.97)        |
| $\omega_{K_D}^2$          | 0.591    | 13.4    | (0.436 - 0.747)      |
| $\omega_{\lambda}^2$      | 1.65     | 14.1    | (1.2 - 2.11)         |
| $\omega_{\text{Base}}^2$  | 0.485    | 7.7     | (0.412 - 0.558)      |

Note: CI: Confidence interval. RSE: Relative standard error. A: Tumor size at time t.  $\hat{K}_L$ : Population tumor growth rate.  $\text{Refractory}_{K_L}$ : Proportional change from  $\hat{K}_L$  for advanced refractory RCC patients.  $\hat{K}_D$ : Population tumor shrinkage rate at median  $C_{\text{avg}}$ , with proportional change of  $C_{\text{avg}K_D}$  for each unit deviation in  $C_{\text{avg}}$ .  $A(\hat{t}=0)$ : Population baseline tumor size if ECOG=1.  $\text{ECOG}0_{A(t=0)}$ : Proportional change in baseline tumor size if ECOG=0.  $\omega_X^2$ : Variance of the inter-individual variability of parameter X.

Source: Table 14 in the PopPK and ER report dated 7/22/2020.

Figure 8. Prediction Corrected Visual Predictive Checks.



**Circles:** Observations, **Solid Blue Line:** Median of the observed tivozanib concentrations, **Dashed Lines:** 5<sup>th</sup> and 95<sup>th</sup> percentiles of the observed tivozanib concentrations, **Shaded Area:** The shaded areas indicate the 90% Confidence Interval (CI) around the prediction-corrected median (green area), and 5<sup>th</sup> and 95<sup>th</sup> percentiles of the simulated concentrations (grey areas). All observations and predictions are adjusted using prediction correction<sup>[9]</sup>.

Source: Figure 11 in the PopPK and ER report dated 7/22/2020.

Progression Free Survival: Cox proportional hazard models were used to assess the effects of tivozanib exposure and covariates on risk of progressive disease. ECOG, study population, and Cavg which was categorized as quartiles were selected as significant covariates in the final model. The parameter estimates were summarized in **Table 40**. The model indicates that the highest tivozanib exposure quartile (Q4) relative to the lowest tivozanib exposure quartile (Q1) was highly statistically significant with an estimated relative risk reduction of approximately 33%. Patients with ECOG status 1 had a 59% higher risk relative to patients with ECOG status 0. Similarly, advanced refractory RCC (AV-951-15-303) patients had a 58% higher risk relative to advanced RCC (AV-951-09-301) patients. However, these results should be interpreted with caution as it was based on data at only one dose level.

Table 40. Summary of Final Tivozanib Cox Proportional Hazard Model of Progression Free Survival

| Variable                                                 | Coefficient | Hazard.Ratio | p.value |
|----------------------------------------------------------|-------------|--------------|---------|
| ECOG=1                                                   | 0.46        | 1.58         | 0.00    |
| Study population advanced refractory RCC (AV-951-15-303) | 0.48        | 1.62         | 0.00    |
| C <sub>avg</sub> Q2                                      | -0.30       | 0.74         | 0.08    |
| C <sub>avg</sub> Q3                                      | -0.44       | 0.65         | 0.01    |
| C <sub>avg</sub> Q4                                      | -0.46       | 0.63         | 0.01    |

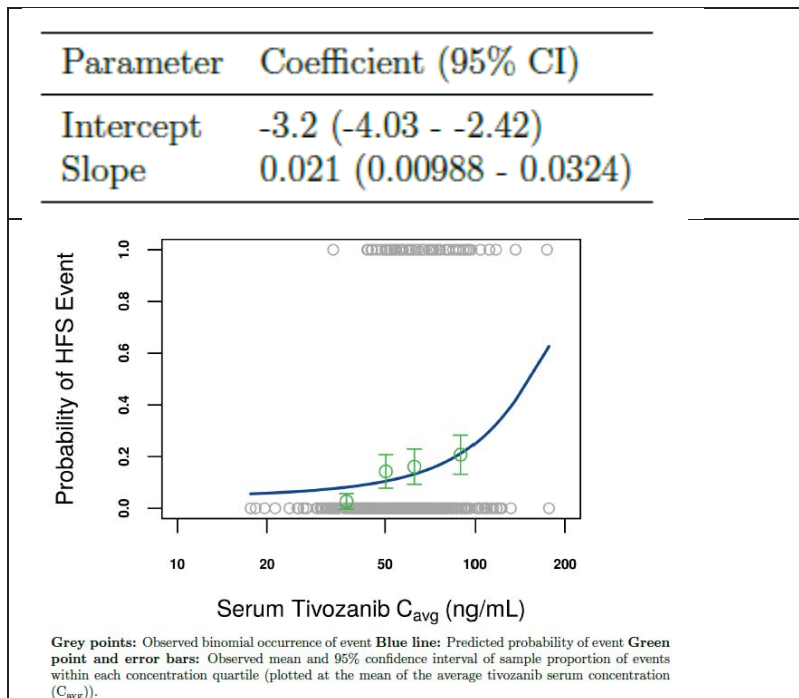
C<sub>avg</sub>: Average concentration; Q<sub>x</sub>: Cavg quartile x (1 to 4); RCC: Renal cell carcinoma

Source: Table 16 in the PopPK and ER report dated 7/22/2020.

### Exposure Safety Response Analyses:

Hand and Foot Syndrome: Logistic regression was used to evaluate the influence of tivozanib exposure data in combination with covariates on the odds of experiencing an HFS event. No significant covariate except for Cavg was selected in the final model. **Table 41** shows parameter estimated from the final model and the plot observed HFS occurrences with model predicted probability vs. Tivozanib Cavg. The result demonstrated exposure-dependent increases in rates of hand-foot syndrome (HFS, a.k.a., palmar-plantar erythrodysesthesia [PPE]).

Table 41. Summary of Final Logistic Regression Model of Effect of Tivozanib Exposure on Odds of Hand and Foot Syndrome.



Source: Table 18 and Figure 24 in the PopPK and ER report dated 7/22/2020.

Blood Pressure: No exposure-response relationship was observed.

### Review Summary

In general, the applicant's population PK analysis is considered acceptable for the purpose of supporting analyses objectives. The applicant's analyses were verified by the reviewer, with no significant discordance identified.

More specifically, the developed model was used to support the current submission as outlined in **Table 42**.

Table 42. Specific Comments on Applicant's Final Population PK model

| Utility of the final model                                                             |                  | Reviewer's Comments                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
|----------------------------------------------------------------------------------------|------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Support applicant's proposed labeling statements about intrinsic and extrinsic factors | Intrinsic factor | <p>"For moderate hepatic impairment (Child-Pugh B), dose with one 1.0 mg capsule taken orally once daily for 21 days on treatment followed by 7 days off treatment for a 28-day cycle. Closely monitor patient."</p> <p>"No relationship has been found between tivozanib PK and serum creatinine and creatinine clearance as measurements of renal function."</p> <p>"Females had a 24.5% lower apparent clearance compared to males independent of body weight. No dose adjustment is required for female patients.</p> <p>The apparent volume of distribution of tivozanib increases nearly proportionally with body weight."</p> <p>"Population pharmacokinetic analysis indicated no clinically relevant effects of age or race on the clearance of tivozanib."</p> |
|                                                                                        | Extrinsic factor | <p>NA</p> <p>The conclusions on extrinsic factors were not based on PopPK analyses.</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
| Derive exposure metrics for Exposure-                                                  | $C_{avg}$        | The applicant's final model is generally acceptable for generating exposure metrics for exposure-response analyses ( <b>Table 36</b> ).                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |

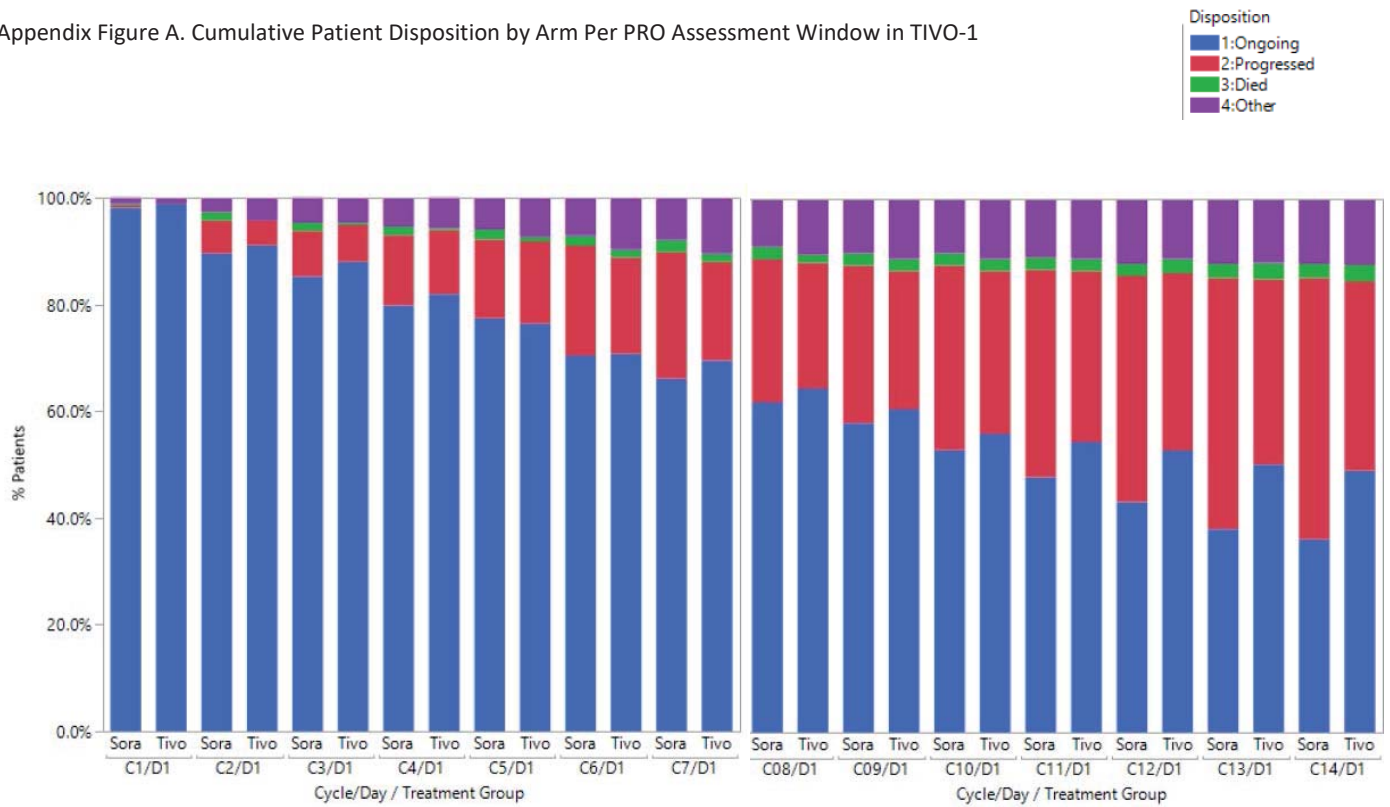
|                                                 |    |                                                                                                                 |
|-------------------------------------------------|----|-----------------------------------------------------------------------------------------------------------------|
| response analyses                               |    | Shrinkage in MTT was high with 60.5% due to sparse data. Caution should be taken when interpreting the results. |
| Predict exposures at alternative dosing regimen | NA | NA                                                                                                              |

## 19.5 Additional Clinical Outcome Assessment Analyses

APPEARS THIS WAY ON ORIGINAL

NDA/BLA Multi-disciplinary Review and Evaluation {NDA 212904}  
 {FOTIVDA, tivozanib}

Appendix Figure A. Cumulative Patient Disposition by Arm Per PRO Assessment Window in TIVO-1



Appendix Table A. FACT-G Questionnaire Completion Rates in TIVO-1, Tivozanib Arm

| Visit Number | Cycle          | N (%) Eligible | At Least One Question Answered | All Questions Answered (EXCEPT GS7)* | All Questions Answered |
|--------------|----------------|----------------|--------------------------------|--------------------------------------|------------------------|
| 2            | CYCLE 1 DAY 1  | 259 (100%)     | 259 (100%)                     | 218 (84%)                            | 132 (51%)              |
| 4            | CYCLE 2 DAY 1  | 256 (98%)      | 254 (99%)                      | 232 (91%)                            | 143 (56%)              |
| 6            | CYCLE 3 DAY 1  | 236 (91%)      | 236 (100%)                     | 213 (90%)                            | 125 (53%)              |
| 7            | CYCLE 4 DAY 1  | 228 (88%)      | 228 (100%)                     | 206 (90%)                            | 128 (56%)              |
| 9            | CYCLE 5 DAY 1  | 212 (81%)      | 209 (99%)                      | 193 (91%)                            | 117 (55%)              |
| 10           | CYCLE 6 DAY 1  | 198 (76%)      | 196 (99%)                      | 188 (95%)                            | 110 (56%)              |
| 12           | CYCLE 7 DAY 1  | 183 (70%)      | 182 (99%)                      | 168 (92%)                            | 101 (55%)              |
| 13           | CYCLE 8 DAY 1  | 180 (69%)      | 179 (99%)                      | 171 (95%)                            | 101 (56%)              |
| 15           | CYCLE 9 DAY 1  | 167 (64%)      | 166 (99%)                      | 156 (93%)                            | 94 (56%)               |
| 16           | CYCLE 10 DAY 1 | 157 (61%)      | 157 (100%)                     | 149 (95%)                            | 86 (55%)               |
| 18           | CYCLE 11 DAY 1 | 145 (56%)      | 144 (99%)                      | 135 (93%)                            | 75 (52%)               |
| 19           | CYCLE 12 DAY 1 | 141 (54%)      | 141 (100%)                     | 130 (92%)                            | 75 (53%)               |
| 21           | CYCLE 13 DAY 1 | 137 (53%)      | 136 (99%)                      | 128 (93%)                            | 71 (52%)               |
| 22           | CYCLE 14 DAY 1 | 130 (50%)      | 130 (100%)                     | 122 (94%)                            | 70 (54%)               |
| 24           | CYCLE 15 DAY 1 | 127 (48%)      | 125 (98%)                      | 117 (92%)                            | 69 (54%)               |
| 25           | CYCLE 16 DAY 1 | 123 (47%)      | 121 (98%)                      | 113 (92%)                            | 65 (53%)               |
| 27           | CYCLE 17 DAY 1 | 120 (46%)      | 119 (99%)                      | 112 (93%)                            | 63 (53%)               |
| 28           | CYCLE 18 DAY 1 | 117 (45%)      | 116 (99%)                      | 110 (94%)                            | 63 (54%)               |
| 30           | CYCLE 19 DAY 1 | 110 (42%)      | 109 (99%)                      | 100 (91%)                            | 56 (51%)               |
| 31           | CYCLE 20 DAY 1 | 101 (39%)      | 100 (99%)                      | 96 (95%)                             | 53 (52%)               |
| 33           | CYCLE 21 DAY 1 | 75 (29%)       | 75 (100%)                      | 71 (95%)                             | 43 (57%)               |
| 34           | CYCLE 22 DAY 1 | 54 (21%)       | 54 (100%)                      | 51 (94%)                             | 31 (57%)               |
| 36           | CYCLE 23 DAY 1 | 39 (15%)       | 39 (100%)                      | 38 (97%)                             | 25 (64%)               |
| 37           | CYCLE 24 DAY 1 | 21 (8%)        | 21 (100%)                      | 21 (100%)                            | 14 (67%)               |
| 39           | CYCLE 25 DAY 1 | 2 (1%)         | 2 (100%)                       | 2 (100%)                             | 2 (100%)               |
| 40           | CYCLE 26 DAY 1 | 0 (---)        | ---                            | ---                                  | ---                    |

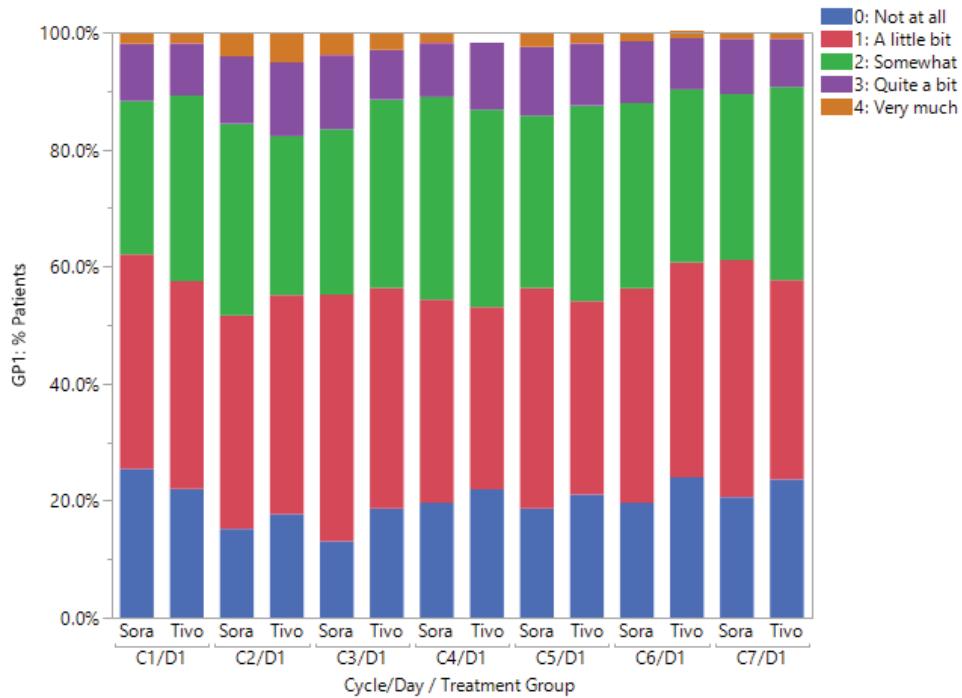
\* Many patients declined to answer question GS7, "I am satisfied with my sex life" since this question is structured with a prior question that states that people are not required to answer it.

Appendix Table B. FACT-G Questionnaire Completion Rates in TIVO-1, Sorafenib Arm

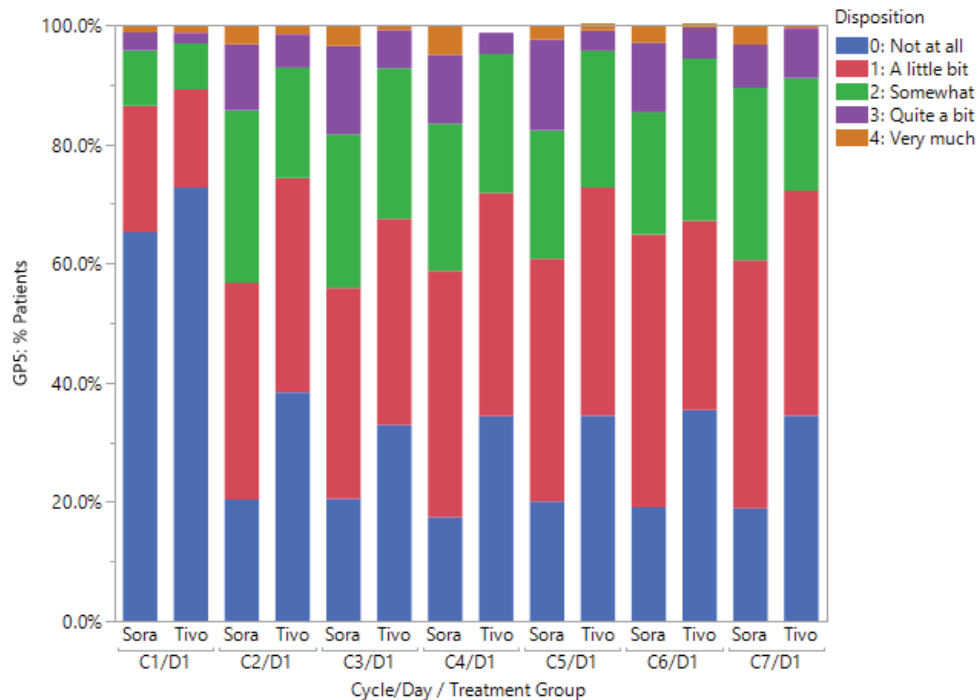
| Visit Number | Cycle          | N (%) Eligible | At Least One Question Answered | All Questions Answered (EXCEPT GS7)* | All Questions Answered |
|--------------|----------------|----------------|--------------------------------|--------------------------------------|------------------------|
| 2            | CYCLE 1 DAY 1  | 257 (100%)     | 256(100%)                      | 219 (85%)                            | 139 (54%)              |
| 4            | CYCLE 2 DAY 1  | 252 (98%)      | 250 (99%)                      | 231 (93%)                            | 144 (57%)              |
| 6            | CYCLE 3 DAY 1  | 230 (89%)      | 230 (100%)                     | 213 (93%)                            | 126 (55%)              |
| 7            | CYCLE 4 DAY 1  | 219 (85%)      | 219 (100%)                     | 202 (92%)                            | 113 (52%)              |
| 9            | CYCLE 5 DAY 1  | 205 (80%)      | 204 (100%)                     | 191 (93%)                            | 112 (55%)              |
| 10           | CYCLE 6 DAY 1  | 199 (77%)      | 199 (100%)                     | 187 (94%)                            | 106 (53%)              |
| 12           | CYCLE 7 DAY 1  | 181 (70%)      | 180 (99%)                      | 170 (94%)                            | 101 (56%)              |
| 13           | CYCLE 8 DAY 1  | 170 (66%)      | 170 (100%)                     | 160 (94%)                            | 93 (55%)               |
| 15           | CYCLE 9 DAY 1  | 159 (62%)      | 158 (99%)                      | 149 (94%)                            | 86 (54%)               |
| 16           | CYCLE 10 DAY 1 | 149 (58%)      | 148 (99%)                      | 138 (93%)                            | 74 (50%)               |
| 18           | CYCLE 11 DAY 1 | 136 (53%)      | 136 (100%)                     | 129 (95%)                            | 66 (49%)               |
| 19           | CYCLE 12 DAY 1 | 123 (48%)      | 123 (100%)                     | 120 (98%)                            | 61 (50%)               |
| 21           | CYCLE 13 DAY 1 | 111 (43%)      | 111 (100%)                     | 108 (97%)                            | 56 (50%)               |
| 22           | CYCLE 14 DAY 1 | 98 (38%)       | 98 (100%)                      | 92 (94%)                             | 46 (47%)               |
| 24           | CYCLE 15 DAY 1 | 93 (36%)       | 93 (100%)                      | 87 (94%)                             | 44 (47%)               |
| 25           | CYCLE 16 DAY 1 | 85 (33%)       | 85 (100%)                      | 80 (94%)                             | 41 (48%)               |
| 27           | CYCLE 17 DAY 1 | 79 (31%)       | 78 (99%)                       | 75 (95%)                             | 37 (47%)               |
| 28           | CYCLE 18 DAY 1 | 72 (28%)       | 72 (100%)                      | 70 (97%)                             | 37 (51%)               |
| 30           | CYCLE 19 DAY 1 | 70 (27%)       | 70 (100%)                      | 67 (96%)                             | 36 (51%)               |
| 31           | CYCLE 20 DAY 1 | 66 (26%)       | 66 (100%)                      | 62 (94%)                             | 34 (52%)               |
| 33           | CYCLE 21 DAY 1 | 59 (23%)       | 59 (100%)                      | 55 (93%)                             | 29 (49%)               |
| 34           | CYCLE 22 DAY 1 | 43 (17%)       | 43 (100%)                      | 40 (93%)                             | 20 (47%)               |
| 36           | CYCLE 23 DAY 1 | 35 (14%)       | 35 (100%)                      | 34 (97%)                             | 15 (43%)               |
| 37           | CYCLE 24 DAY 1 | 25 (10%)       | 25 (100%)                      | 24 (96%)                             | 10 (40%)               |
| 39           | CYCLE 25 DAY 1 | 13 (5%)        | 13 (100%)                      | 13 (100%)                            | 7 (54%)                |
| 40           | CYCLE 26 DAY 1 | 3 (1%)         | 3 (100%)                       | 3 (100%)                             | 1 (33%)                |

\* Many patients declined to answer question GS7, " I am satisfied with my sex life" since this question is structured with a prior question that states that people are not required to answer it

Appendix Figure B. Responses to “I Have a Lack of Energy” (Item GP1) by Treatment Arm



Appendix Figure C. Responses to “I Am Bothered by Side Effects of Treatment” (Item GP5) by Treatment Arm



## Signatures

| DISCIPLINE                        | REVIEWER                                                                                                                                                                                                                                                                                                                                   | OFFICE/DIVISION | SECTIONS AUTHORED/ APPROVED | AUTHORED/ APPROVED                                                                                                 |
|-----------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------|-----------------------------|--------------------------------------------------------------------------------------------------------------------|
| Nonclinical Reviewer              | Eias Zahalka                                                                                                                                                                                                                                                                                                                               | OOD/DHOT        | Sections: 5, 11, 19.3       | <b>Select one:</b><br><input checked="" type="checkbox"/> Authored<br><input checked="" type="checkbox"/> Approved |
|                                   | <b>Signature:</b> Eias A. Zahalka -S<br><small>Digitally signed by Eias A. Zahalka -S<br/>           DN: c=US, o=U.S. Government, ou=HHS, ou=FDA,<br/>           ou=People, 0.9.2342.19200300.100.1.1=2001008670,<br/>           cn=Eias A. Zahalka -S<br/>           Date: 2021.03.10 10:27:41 -05'00'</small>                            |                 |                             |                                                                                                                    |
| Nonclinical Team Leader           | Tiffany Ricks                                                                                                                                                                                                                                                                                                                              | OOD/DHOT        | Sections: 5, 11, 19.3       | <b>Select one:</b><br><input type="checkbox"/> Authored<br><input checked="" type="checkbox"/> Approved            |
|                                   | <b>Signature:</b> Tiffany K. Ricks -S<br><small>Digitally signed by Tiffany K. Ricks -S<br/>           DN: c=US, o=U.S. Government, ou=HHS, ou=FDA,<br/>           ou=People,<br/>           0.9.2342.19200300.100.1.1=2000497170,<br/>           cn=Tiffany K. Ricks -S<br/>           Date: 2021.03.10 08:46:31 -05'00'</small>          |                 |                             |                                                                                                                    |
| Division Director (DHOT)          | John Leighton                                                                                                                                                                                                                                                                                                                              | OOD/DHOT        | Sections: 5, 11, 19.3       | <b>Select one:</b><br><input type="checkbox"/> Authored<br><input checked="" type="checkbox"/> Approved            |
|                                   | <b>Signature:</b> John K. Leighton -S<br><small>Digitally signed by John K. Leighton -S<br/>           DN: c=US, o=U.S. Government, ou=HHS, ou=FDA,<br/>           ou=People, 0.9.2342.19200300.100.1.1=1300085260,<br/>           cn=John K. Leighton -S<br/>           Date: 2021.03.10 10:43:08 -05'00'</small>                         |                 |                             |                                                                                                                    |
| Clinical Pharmacology Reviewer    | Miao Zhao                                                                                                                                                                                                                                                                                                                                  | OCP/DCPI        | Sections: 6, 11, 19.4       | <b>Select one:</b><br><input checked="" type="checkbox"/> Authored<br><input type="checkbox"/> Approved            |
|                                   | <b>Signature:</b> Miao Zhao -S<br><small>Digitally signed by Miao Zhao -S<br/>           DN: c=US, o=U.S. Government, ou=HHS,<br/>           ou=FDA, ou=People, cn=Miao Zhao -S,<br/>           0.9.2342.19200300.100.1.1=2002979628<br/>           Date: 2021.03.10 11:16:13 -05'00'</small>                                              |                 |                             |                                                                                                                    |
| Clinical Pharmacology Team Leader | Jeanne Fourie Zirkelbach                                                                                                                                                                                                                                                                                                                   | OCP/DCPII       | Sections: 6, 11, 19.4       | <b>Select one:</b><br><input type="checkbox"/> Authored<br><input checked="" type="checkbox"/> Approved            |
|                                   | <b>Signature:</b> Jeanne Fourie Zirkelbach -S<br><small>Digitally signed by Jeanne Fourie Zirkelbach -S<br/>           DN: c=US, o=U.S. Government, ou=HHS, ou=FDA,<br/>           ou=People, 0.9.2342.19200300.100.1.1=1300434575,<br/>           cn=Jeanne Fourie Zirkelbach -S<br/>           Date: 2021.03.10 12:08:52 -05'00'</small> |                 |                             |                                                                                                                    |

| DISCIPLINE                              | REVIEWER                                                                                                                                                                                                                                                                | OFFICE/DIVISION | SECTIONS AUTHORED/ APPROVED | AUTHORED / APPROVED                                                                                                |
|-----------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------|-----------------------------|--------------------------------------------------------------------------------------------------------------------|
| Clinical Pharmacology Division Director | Nam Atiqur Rahman                                                                                                                                                                                                                                                       | OCP/DCPII       | Sections: 6, 11, 19.4       | <b>Select one:</b><br><input type="checkbox"/> Authored<br><input checked="" type="checkbox"/> Approved            |
|                                         | <b>Signature: Nam A. Rahman -S</b><br><small>Digitally signed by Nam A. Rahman -S<br/> DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People,<br/> cn=Nam A. Rahman -S, 0.9.2342.19200300.100.1.1=1300072597<br/> Date: 2021.03.10 11:00:58 -05'00'</small>            |                 |                             |                                                                                                                    |
| Pharmacometrics Reviewer                | Junshan Qiu                                                                                                                                                                                                                                                             | OCP/DPM         | Sections: 19.4              | <b>Select one:</b><br><input checked="" type="checkbox"/> Authored<br><input type="checkbox"/> Approved            |
|                                         | <b>Signature: Junshan Qiu -S</b><br><small>Digitally signed by Junshan Qiu -S<br/> DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, ou=Junshan Qiu -S<br/> 0.9.2342.19200300.100.1.1=2000388577<br/> Date: 2021.03.10 09:20:38 -05'00'</small>                   |                 |                             |                                                                                                                    |
| Pharmacometrics Team Leader             | Jingyu Yu                                                                                                                                                                                                                                                               | OCP/DPM         | Sections:19.4               | <b>Select one:</b><br><input checked="" type="checkbox"/> Authored<br><input checked="" type="checkbox"/> Approved |
|                                         | <b>Signature: Jingyu Yu -S</b><br><small>Digitally signed by Jingyu Yu -S<br/> DN: c=US, o=U.S. Government, ou=HHS, ou=FDA,<br/> ou=People, cn=Jingyu Yu -S,<br/> 0.9.2342.19200300.100.1.1=2000794699<br/> Date: 2021.03.10 10:35:56 -05'00'</small>                   |                 |                             |                                                                                                                    |
| Bioanalytical Method Reviewer           | Amanda Lewin                                                                                                                                                                                                                                                            | OSIS/DNDSI      | Sections: 19.4              | <b>Select one:</b><br><input checked="" type="checkbox"/> Authored<br><input type="checkbox"/> Approved            |
|                                         | <b>Signature: Amanda E. Lewin -S</b><br><small>Digitally signed by Amanda E. Lewin -S<br/> DN: c=US, o=U.S. Government, ou=HHS, ou=FDA,<br/> ou=People, 0.9.2342.19200300.100.1.1=2002000530,<br/> cn=Amanda E. Lewin -S<br/> Date: 2021.03.10 10:32:38 -05'00'</small> |                 |                             |                                                                                                                    |
| QT/IRT Reviewer                         | Girish Bende                                                                                                                                                                                                                                                            | OCP/DCEP        | Sections: 6.3 & 8.2.4       | <b>Select one:</b><br><input checked="" type="checkbox"/> Authored<br><input type="checkbox"/> Approved            |
|                                         | <b>Signature: Girish K. Bende -S</b><br><small>Digitally signed by Girish K. Bende -S<br/> DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People,<br/> 0.9.2342.19200300.100.1.1=2002119970, cn=Girish K. Bende -S<br/> Date: 2021.03.10 10:48:27 -05'00'</small>      |                 |                             |                                                                                                                    |
| QT/IRT Reviewer                         | Raman Baweja                                                                                                                                                                                                                                                            | OCP/DPM         | Sections: 6.3 & 8.2.4       | <b>Select one:</b><br><input checked="" type="checkbox"/> Authored<br><input type="checkbox"/> Approved            |
|                                         | <b>Signature: Raman K. Baweja -S</b><br><small>Digitally signed by Raman K. Baweja -S<br/> DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People,<br/> 0.9.2342.19200300.100.1.1=1300040883, cn=Raman K. Baweja -S<br/> Date: 2021.03.10 10:21:31 -05'00'</small>      |                 |                             |                                                                                                                    |

| DISCIPLINE                            | REVIEWER                                                                                                                                                                                                                                                                    | OFFICE/DIVISION | SECTIONS AUTHORED/ APPROVED                                | AUTHORED/ APPROVED                                                                                                 |
|---------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------|------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------|
| Clinical Reviewer                     | Elaine Chang                                                                                                                                                                                                                                                                | OOD/DO1         | Sections: 2-4, 7-13                                        | <b>Select one:</b><br><input checked="" type="checkbox"/> Authored<br><input type="checkbox"/> Approved            |
|                                       | <b>Signature: Elaine Chang -S</b><br><small>Digitally signed by Elaine Chang -S<br/> DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Elaine Chang -S,<br/> 0.9.2342.19200300.100.1.1=2002602609<br/> Date: 2021.03.10 09:11:53 -05'00'</small>                   |                 |                                                            |                                                                                                                    |
| Statistical Reviewer                  | Lijun Zhang                                                                                                                                                                                                                                                                 | OB/DBV          | Sections: 8                                                | <b>Select one:</b><br><input checked="" type="checkbox"/> Authored<br><input type="checkbox"/> Approved            |
|                                       | <b>Signature: Lijun Zhang -S</b><br><small>Digitally signed by Lijun Zhang -S<br/> DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Lijun Zhang -S,<br/> 0.9.2342.19200300.100.1.1=2000472119<br/> Date: 2021.03.10 09:25:12 -05'00'</small>                      |                 |                                                            |                                                                                                                    |
| Statistical Team Leader               | Mallorie Fiero                                                                                                                                                                                                                                                              | OB/DBV          | Sections: 8                                                | <b>Select one:</b><br><input checked="" type="checkbox"/> Authored<br><input checked="" type="checkbox"/> Approved |
|                                       | <b>Signature: Mallorie H. Fiero -S</b><br><small>Digitally signed by Mallorie H. Fiero -S<br/> DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People,<br/> 0.9.2342.19200300.100.1.1=2002084959, cn=Mallorie H. Fiero -S<br/> Date: 2021.03.10 09:07:52 -05'00'</small>    |                 |                                                            |                                                                                                                    |
| Division Director (OB)                | Shenghui Tang                                                                                                                                                                                                                                                               | OB/DBV          | Sections: 8                                                | <b>Select one:</b><br><input type="checkbox"/> Authored<br><input checked="" type="checkbox"/> Approved            |
|                                       | <b>Signature: Shenghui Tang -S</b><br><small>Digitally signed by Shenghui Tang -S<br/> DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People,<br/> cn=Shenghui Tang -S, 0.9.2342.19200300.100.1.1=1300224175<br/> Date: 2021.03.10 08:20:24 -05'00'</small>                |                 |                                                            |                                                                                                                    |
| Associate Director for Labeling (ADL) | William Pierce                                                                                                                                                                                                                                                              | OCE/OOD         | Sections: 11, Prescribing Information, Patient Information | <b>Select one:</b><br><input checked="" type="checkbox"/> Authored<br><input checked="" type="checkbox"/> Approved |
|                                       | <b>Signature: William F. Pierce -S5</b><br><small>Digitally signed by William F. Pierce -S5<br/> DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People,<br/> 0.9.2342.19200300.100.1.1=1300235575, cn=William F. Pierce -S5<br/> Date: 2021.03.10 10:05:45 -05'00'</small> |                 |                                                            |                                                                                                                    |

| DISCIPLINE                            | REVIEWER                                                                                                                                                                                                                                                                                                                                        | OFFICE/DIVISION | SECTIONS AUTHORED/ APPROVED  | AUTHORED/ APPROVED                                                                                                 |
|---------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------|------------------------------|--------------------------------------------------------------------------------------------------------------------|
| Cross-Disciplinary Team Leader (CDTL) | Chana Weinstock                                                                                                                                                                                                                                                                                                                                 | OOD/DO1         | Section 1:<br>Sections 1-17: | <b>Select one:</b><br><input checked="" type="checkbox"/> Authored<br><input checked="" type="checkbox"/> Approved |
|                                       | <b>Signature:</b> Chana Weinstock -S  Digitally signed by Chana Weinstock -S<br>DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2001659606, cn=Chana Weinstock -S<br>Date: 2021.03.10 12:12:53 -05'00'                       |                 |                              |                                                                                                                    |
| Division Director (Clinical)          | Laleh Amiri-Kordestani                                                                                                                                                                                                                                                                                                                          | OOD/DO1         | Sections:1-17                | <b>Select one:</b><br><input type="checkbox"/> Authored<br><input checked="" type="checkbox"/> Approved            |
|                                       | <b>Signature:</b> Laleh Amiri-kordestani -S  Digitally signed by Laleh Amiri kordestani -S<br>DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=0014338688, cn=Laleh Amiri kordestani -S<br>Date: 2021.03.10 08:30 48. 05'00' |                 |                              |                                                                                                                    |
| Office Director                       | Julia Beaver                                                                                                                                                                                                                                                                                                                                    | OCE             | Sections: 1-17               | <b>Select one:</b><br><input type="checkbox"/> Authored<br><input checked="" type="checkbox"/> Approved            |
|                                       | <b>Signature:</b> {See appended electronic signature page}                                                                                                                                                                                                                                                                                      |                 |                              |                                                                                                                    |

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**This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.**  
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/s/  
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JESSICA KIM  
03/10/2021 12:26:31 PM

JULIA A BEAVER  
03/10/2021 01:33:35 PM