The Effect of Food on the Pharmacokinetics of Tivozanib

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Introduction

- Tivozanib (AV-951) is a potent, selective, long half-life ($t_{1/2}$), small-molecule tyrosine kinase inhibitor of the vascular endothelial growth factor receptors 1, 2, and 3[1]
- Results from a Phase I study in patients with cancer determined the maximum tolerated dose of tivozanib to be 1.5 mg/day[1]
- Tivozanib has demonstrated anti-tumor activity in a Phase II study and a recent Phase III study in patients with renal cell carcinoma (RCC),[2,3] and is currently being studied in Phase I/II studies of patients with other solid tumors
- The pharmacokinetics (PK) of tivozanib have been evaluated across various studies of healthy volunteers[4] and patients with cancer[1,2,4–6]
  - Median time to peak serum concentration (T_{max}) ranges from ~2 to 24 hours with substantial variability among subjects,[1,2,6] most likely due to enterohepatic recirculation
  - Accumulation at steady state is ~6 to 7 times single-dose levels.[1] This accumulation is consistent with the long mean $t_{1/2}$ of tivozanib (~3.6–4.7 days)[1,2,4]
  - The PK profile of tivozanib is similar in healthy volunteers and patients with cancer[4]
- This Phase I study was conducted to prospectively evaluate the effect of food on the PK of a single 1.5 mg dose of tivozanib in healthy subjects

Objectives

- To determine the effect of food on the PK of a single dose of 1.5 mg tivozanib in healthy subjects
- To assess the tolerability of a single dose of 1.5 mg tivozanib in healthy subjects

Methods

Key Eligibility Criteria

- Healthy males or females aged 18–55 years
- Body mass index (BMI) 18.5–31.0 kg/m^2
- No clinically significant findings from medical history, physical examination, vital signs, electrocardiogram (ECG), or laboratory assessments
- Subjects with blood pressure greater than 140/90 mmHg were excluded
- Subjects were prohibited from use of prescription medications and over-the-counter preparations

Study Design and Treatment

- This was a single-center, open-label, randomized, two-period, crossover Phase I study conducted at Covance Clinical Research Unit in Dallas, Texas, USA **(Table 1)**
- Subjects were screened for eligibility up to 28 days prior to study entry and were randomly assigned to 1 of the following sequences on Day 1 of Period 1:
  - Sequence 1: treatment with a single oral dose of 1.5 mg tivozanib in the fasted state (approximate 10-hour fast) followed by a 6-week washout period, then treatment with a single oral dose of 1.5 mg tivozanib in the fed state (after a standard US Food and Drug Administration high-fat breakfast)
  - Sequence 2: treatment with a single oral dose of 1.5 mg tivozanib in the fed state followed by a 6-week washout period, then treatment with a single oral dose of 1.5 mg tivozanib in the fasted state
- For each study period of the sequence, subjects were admitted to the clinical research unit (CRU) 1 day before dosing and fasted ~10 hours
- Subjects remained at the CRU for at least 48 hours post-dose for blood sample collection and safety monitoring, and returned to the CRU on an outpatient basis for collection of additional blood samples for up to 504 hours post-dose
  - PK blood samples were collected at the following time points for each study period of the sequence: 0 hour (predose), 1, 3, 5, 7, 10, 12, 18, 24, 36, 48, 96, 168, 336, and 504 hours post-dose
- Physical examinations, ECGs, vital signs, How Do You Feel? (HDYF?) inquiries, and clinical laboratory evaluations were performed at screening and/or at specified times during the study
- All adverse events (AE) were recorded throughout the study until study completion

Table 1. Study Design

Period 1					Period 2			End of Study
Screening	Check-in	Dosing	Outpatient Visits	6-week washout	Check-in	Dosing	Outpatient Visits	Outpatient Visit
2–28 days prior to dosing	1 day prior to dosing	Day 1	Days 5, 8, 15, and 22		Day 42	Day 43	Days 47, 50, and 57	Day 64
	Subject Confinement ≥48 hrs post-dose				Subject Confinement ≥48 hrs post-dose			

Pharmacokinetics and Statistical Analysis

- The PK parameters evaluated were maximal serum concentration (C_{max}), T_{max}, $t_{1/2}$, area under the concentration–time curve extrapolated to infinity ($AUC_{0-\infty}$), apparent total clearance (CL/F), and apparent volume of distribution (Vz/F)
- PK data were analyzed by non-compartmental methods using Phoenix WinNonlin, version 5.2 (Pharsight Corporation, Cary, NC, USA)
- The effect of food on PK was assessed between fed state and fasted state using an analysis of variance and standard criteria for bioequivalence based on the exposure parameters $AUC_{0-\infty}$ and C_{max}
  - If the 90% confidence intervals (CIs) for the fed/fasted $AUC_{0-\infty}$ and C_{max} were to fall within the range of 80–125%, it was to be concluded that food had no effect on exposure
  - Calculations were performed using Statistical Analysis Software, version 9.1.3 (SAS Institute Inc, Cary, NC, USA)
- Determination of sample size: with 24 subjects completing the trial, this crossover design would have ≥90% power with two-sided, type-I error rate of 5% to reject the null hypothesis that tivozanib exposure was not equivalent between fed and fasted states

Results

Subjects

- Thirty healthy volunteers were enrolled in the study **(Table 2)**
  - Subjects had a mean age of 39 years
- Twenty-nine subjects (97%) completed the study
  - One subject was lost to follow-up at 22 days after dosing in the fed state during Period 1 of Sequence 2

Table 2. Subject Demographics

Characteristic	N=30
Mean age (range), yrs	39 (22–53)
Mean weight (range), kg	75.7 (55.5–105.2)
Mean BMI (range), kg/m^2	26.0 (21.4–30.8)
Gender, n (%)	
Male	19 (63)
Female	11 (37)
Ethnicity, n (%)	
Hispanic or Latino	15 (50)
Not Hispanic or Latino	15 (50)
Race, n (%)	
White	21 (70)
Black	8 (27)
American Indian	1 (3)

Pharmacokinetics

- Food delayed absorption of tivozanib and caused a significant decrease in maximal serum tivozanib levels vs fasted state **(Tables 3 and 4; Figures 1 and 2)**
  - Following a single oral dose of 1.5 mg tivozanib, median T_{max} was longer in the fed state (24.0 hours), compared with that in the fasted state (3.0 hours) **(Table 3 and Figure 1)**
  - The mean C_{max} values in the fed state were lower than that achieved in the fasted state (geometric means, 14.1 and 18.1 ng/mL, respectively) **(Table 3 and Figure 2)**
  - The geometric mean ratio (90% CI) of fed relative to fasted states for C_{max} was 77.5% (72.9–82.4%); the 90% CI did not fall within the 80–125% bioequivalence range **(Table 4)**
- Despite the decrease in serum concentration, there was no significant difference in $AUC_{0-\infty}$ of serum tivozanib between the fed and fasted states **(Tables 3 and 4; Figure 3)**
  - The mean $AUC_{0-\infty}$ was similar between the fed and fasted states (geometric means, 2377 ng·hr/mL and 2198 ng·hr/mL respectively) **(Table 3 and Figure 3)**
  - The geometric mean ratio (90% CI) of fed relative to fasted states for $AUC_{0-\infty}$ was 107.4% (102.8–112.3%); the 90% CI was within the 80–125% bioequivalence range **(Table 4)**
- Food did not appear to have an impact on the elimination of tivozanib **(Table 3)**
  - The mean $t_{1/2}$, CL/F, and Vz/F values for tivozanib were similar in the fed and fasted states **(Table 3)**

Table 3. Pharmacokinetic Parameters for Serum Tivozanib in the Fed or Fasted State

Parameter, geometric mean[a,b]	Fed	Fasted
$AUC_{0-\infty}$, ng·hr/mL	2377 (n=29)	2198 (n=28)[c]
C_{max}, ng/mL	14.1 (n=30)	18.1 (n=29)
T_{max}, hr[a] (range)	24.0 (5.0–48.0) (n=30)	3.0 (3.0–96.0) (n=29)
$t_{1/2}$, hr[b] ± SD	122±31.1 (n=29)	121±29.9 (n=28)[c]
CL/F, L/hr	0.564 (n=29)	0.610 (n=28)[c]
Vz/F, L	96.3 (n=29)	103 (n=28)[c]

[a] Median (min, max) is presented for T_{max}.
[b] Arithmetic mean is presented for $t_{1/2}$.
[c] One subject had no distinct terminal elimination phase, so $t_{1/2}$, as well as other related PK parameters such as $AUC_{0-\infty}$, CL/F, and Vz/F, could not be calculated.

Table 4. Statistical Analysis for C_{max} and $AUC_{0-\infty}$ of Serum Tivozanib

	LS mean fed	LS mean fasted	LS mean ratio (fed/fasted)	90% CI
C_{max}, ng/mL	14.1 (n=30)	18.2 (n=29)	77.5%	72.9–82.4%
$AUC_{0-\infty}$, ng·hr/mL	2372 (n=29)	2209 (n=28)	107.4%	102.8–112.3%

LS, least squares.

Figure 1. Arithmetic mean serum concentration–time profiles for tivozanib in the fed or fasted state.

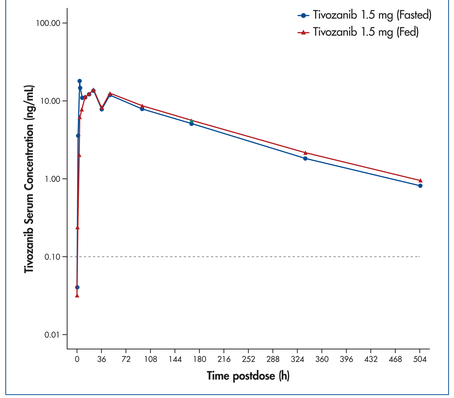


Figure 2. Individual and arithmetic mean C_{max} following a single oral dose of 1.5 mg tivozanib in the fed or fasted state.

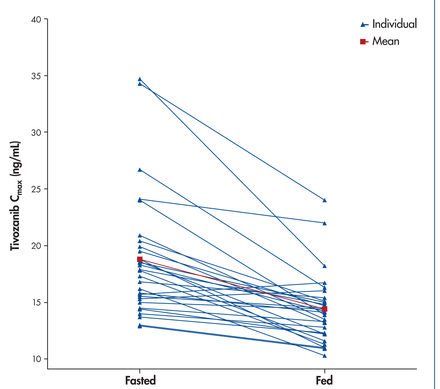
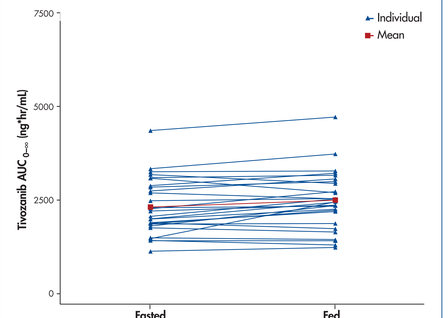


Figure 3. Individual and arithmetic mean $AUC_{0-\infty}$ following a single oral dose of 1.5 mg tivozanib in fed or fasted state.



Tolerability

- Twelve subjects reported a total of 25 AEs during the study
  - All 25 AEs were mild in intensity
  - Seventeen AEs occurred in the fed state, and 8 occurred in the fasted state
  - Three AEs were considered possibly related to tivozanib: headache was reported by two subjects in the fed state, and nausea was reported by one subject in the fasted state
- No clinically significant changes or findings in clinical laboratory evaluations, vital signs measurements, physical examinations, or ECGs were noted

Conclusions

- Dosing tivozanib with food decreases maximal concentrations (C_{max}) by ~23%, but does not affect overall exposure (AUC)
- Administration of a single oral dose of 1.5 mg tivozanib was well tolerated in this group of healthy subjects
- As tivozanib is dosed chronically in oncology patients and accumulates ~6 to 7 times single-dose levels when at steady state,[1] lack of an overall effect of food on the AUC of tivozanib, even with a decrease in C_{max}, is unlikely to have an impact on steady-state serum concentrations
- Overall, these results indicate that food does not have a clinically meaningful effect on the PK of tivozanib as compared with dosing in the fasted state

References

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Acknowledgments

This study was supported by AVEO Pharma Inc. and Astellas Pharma Global Development, Inc. AVEO and Astellas are parties to a collaboration agreement for the co-development of tivozanib. Editorial assistance was provided by Jinling Wu, MD, PhD, Chameleon Communications International, and was funded by AVEO Pharma Inc. and Astellas Scientific and Medical Affairs, Inc.

POSTER PRESENTED AT THE 2012 AMERICAN ASSOCIATION FOR CANCER RESEARCH (AACR) ANNUAL MEETING; CHICAGO, IL; MARCH 31–APRIL 4, 2012.