Abstract # C123

A Phase I Study to Evaluate the Absorption, Metabolism and Excretion of the Vascular Endothelial Growth Factor Receptor (VEGFR) Tyrosine Kinase Inhibitor (TKI), Tivozanib

Monette M. Cotreau[1], Christine L. Hale[2], Lindsey Jacobson[1], Claudine S. Oelke[2], Andrew L. Strahs[1], Robert G. Kochan[2], William Slichenmyer[1], Dennis L. Vargo[1]

[1]AVEO Pharmaceuticals, Cambridge, MA, USA; [2]Covance Clinical Research Unit, Madison, WI, USA

Introduction

- Tivozanib is a potent, selective, long half-life tyrosine kinase inhibitor of vascular endothelial growth factor receptors (VEGFRs) -1,- 2, and -3 that is currently being developed for the treatment of renal cell carcinoma (RCC) and other solid malignancies[1]
- The VEGF pathway plays a significant role in angiogenesis, an essential mechanism by which many tumors thrive[2]
- The pharmacokinetics (PK) of tivozanib have been evaluated across various studies of healthy volunteers[3] and patients with cancer[3-8]
  - Median time to peak serum concentration (T_{max}) ranges from ~2 to 24 hours with substantial variability among subjects, most likely due to enterohepatic recirculation
  - Exposure (maximum concentration [C_{max}] and area under the concentration–time curve [AUC]) of tivozanib generally increases in a dose proportional manner
  - Accumulation at steady state is ~6 to 7 times single-dose levels. This accumulation is consistent with the long, mean half-life ($t_{1/2}$) of tivozanib (~3.6–5.0 days)
  - The PK profile of tivozanib is similar in healthy volunteers and patients with cancer

Objective

- This study was conducted to determine the absorption, metabolism, and excretion of a single 1.5 mg dose of [^{14}C]-tivozanib (equivalent to 1.34 mg [^{14}C]-tivozanib–free base) administered to healthy male subjects

Methods

Key Eligibility Criteria

- Males in good health aged 18 to 55 years who were sterile or had documented contraception use
- Body mass index 18.5 to 31.0 kg/m^2
- No clinically significant findings on physical examination, vital signs, electrocardiogram (ECG), or in laboratory assessments
- At least one bowel movement per day

Study Design

- A single-center, open-label, non-randomized, Phase I clinical trial conducted at Covance Clinical Research Unit, Madison, WI, USA (**Table 1**)
- Subjects were administered a single 1.5 mg (~160 µCi) dose of [^{14}C]-tivozanib orally in a fasted state
- Physical examinations, ECGs, vital signs, and clinical laboratory evaluations were performed prior to enrollment, at specified times during the study, and at study completion

Table 1. Study Design

Screening	Check-in	Dosing	Pharmacokinetic/Radioactivity/Metabolite Sampling (blood, urine, feces)	Study Completion
2 to 28 days prior to dosing	1 day prior to dosing	Day 1	Day 1 to 21[a]	Day 21 to 29
← Subject Confinement →				

[a]Pharmacokinetic (PK) and radioactivity sampling was continued until study completion, which could have extended until Day 29.

Study Assessments

- Whole blood, serum, urine, and feces were evaluated for up to 28 days post dose for assessment of total radioactivity and [^{14}C]-tivozanib concentrations
  - Blood samples for PK analysis and radioanalysis were collected via direct venipuncture at the following time points: 0-hour (predose); 1, 3, 5, 7, 10, 14, 18, 24, 36, 48, and 72 hours post dose; and at 24-hour intervals until study completion
  - Blood samples for metabolite profiling and identification were collected via direct venipuncture at 0-hour (predose) and 7, 14, 24, 36, 48, 72, 96, 120, 192, 264, 360, 456, 552, and 648 hours post dose; the minimum collection period was 21 days post dose
  - Urine samples were collected for radioanalysis and metabolite profiling over the following intervals: -12 to 0 (predose); 0 to 6, 6 to 12, and 12 to 24 hours post dose; and at 24-hour intervals until study completion
  - Fecal samples for radioanalysis and metabolite profiling were collected predose and at 24-hour intervals post dose until study completion

Pharmacokinetics

- PK parameters evaluated were C_{max}, T_{max}, $t_{1/2}$, apparent total clearance (CL/F), and area under the concentration-time curve extrapolated to infinity ($AUC_{0-\infty}$)
- PK parameters were determined by non-compartmental methods using Phoenix WinNonlin, version 5.2 (Pharsight Corporation, Cary, NC, United States)

Radioanalysis

- All samples were analyzed for radioactivity in Model 2900TR liquid scintillation counters for at least 5 minutes or 100,000 counts
- Feces were homogenized in acetonitrile:water (1:1, v:v). All samples were analyzed in duplicate (sample size allowing) and counted for at least 5 minutes or 100,000 counts

Metabolite Profile

- Available metabolite structures were identified by liquid chromatography mass spectrometry (LC-MS and/or LC-MS/MS) methods

Safety

- All adverse events (AEs) volunteered, elicited, or noted on physical examination were recorded throughout the study from informed consent until study completion, coded using the *Medical Dictionary for Regulatory Activities* (MedDRA) version 13.0, and summarized using MedDRA System Organ Class and preferred term

Statistical Analysis

- Descriptive statistics for radioanalysis data were compiled using Excel version 11.0 (Microsoft Corporation, Redmond, WA, United States)
  - Radioanalysis data and dose tables were compiled using data from Debra, version 5.7.8 (LabLogic Systems Ltd., Sheffield, United Kingdom) with mean and standard deviation (SD) values calculated using Excel
- Descriptive statistics were compiled for PK and safety data using Statistical Analysis Software (SAS®; SAS Institute Inc., Cary, NC, United States) version 9.1 or greater
- No formal statistical analysis was planned

Results

- A total of eight healthy male subjects were enrolled in the study (**Table 2**)
  - Subjects had a median age of 31 years
- Seven (87.5%) subjects completed the study
  - One subject voluntarily withdrew from the study on Day 20

Table 2. Subject Demographics

Characteristic	N=8
Age, mean ± SD (range), y	32 ± 8.7 (19–46)
Weight, mean ± SD (range), kg	80 ± 9.6 (66–99)
BMI, mean ± SD (range), kg/m^2	25 ± 1.9 (23–29)
Ethnicity, n (%)	
Hispanic or Latino	3 (37.5)
Not Hispanic or Latino	5 (62.5)
Race, n (%)	
White	6 (75)
Black	2 (25)

BMI, body mass index.

Pharmacokinetics

- The serum concentration of [^{14}C]-tivozanib peaked at approximately 10 hours after oral administration (**Figure 1**)
- Mean blood-to-serum concentration ratios ranged from 0.495 to 0.615 through 312 hours post dose, indicating minimal association of radioactivity with red blood cells
- The mean half-life for [^{14}C]-tivozanib was ~3.7 days (**Table 3**)

Radioanalysis

- Overall, mean ± SD recovery of total radioactivity was 91.1% ± 11.0%, with 11.8% ± 4.6% recovered in urine and 79.3% ± 8.8% recovered in feces (**Figure 2**)

Figure 1. Mean serum concentration–time profiles for [^{14}C]-tivozanib in serum and total radioactivity in serum and whole blood.

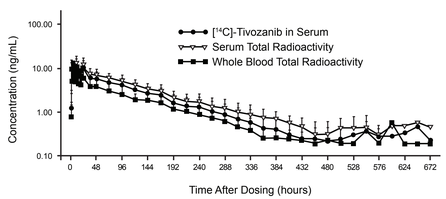
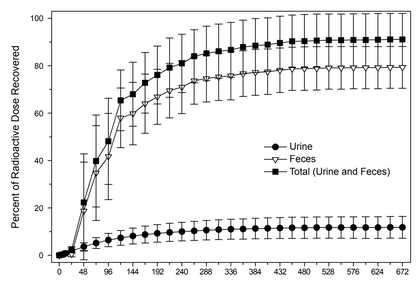


Table 3. Pharmacokinetic Parameters for [^{14}C]-Tivozanib and Total Radioactivity in Serum

PK Parameter*	[^{14}C]-Tivozanib	Total Radioactivity
C_{max} (SD), ng/mL	12.1 (5.67)	13.0 (6.24)
T_{max} (SD), hr	10.9 (5.84)	12.6 (7.42)
$AUC_{0-\infty}$ (SD), ng*hr/mL	1084 (417.0)	1355 (460.0)
$t_{1/2}$ (SD), hr	89.3 (23.50)	99.1 (32.50)
CL/F (SD), L/hr	1.45 (0.652)	1.24 (0.480)

hr, hours.
*Mean values of PK parameters.

Figure 2. Cumulative percent dose recovered in urine and feces of [^{14}C]-tivozanib.



Metabolites

Serum

- The major circulating component in the serum was unchanged [^{14}C]-tivozanib, ranging from 77.6% to 95.1% of the total radioactivity in the high performance liquid chromatography (HPLC) run (**Figure 3**)
- Minor unknown metabolites detected accounted for a total mean of ≤4% of the total radioactivity in the HPLC run

Feces

- The major radiolabeled components detected in fecal extracts were unchanged [^{14}C]-tivozanib (7.82% to 46.1% of the radioactive dose in the samples), metabolites M37 (desmethoxyl-tivozanib), M42 (structure not proposed), and M7 (desmethyl-tivozanib)/M48 (structure not proposed) co-eluting (**Figure 4**). The major metabolites represented a total of 6.35% to 34.3% of the radioactive dose in the analyzed samples

Figure 3. Metabolite radioprofile from a 7- to 120-hour pooled serum sample after a single oral dose of [^{14}C]-tivozanib to a representative subject (1.5 mg, ~160 µCi).

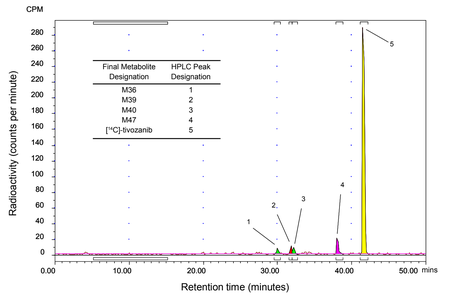
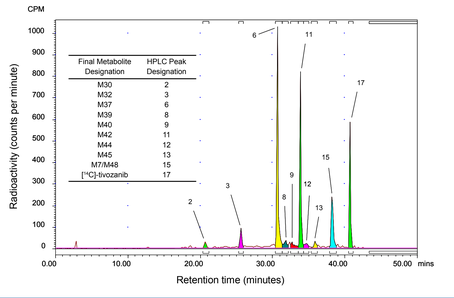


Figure 4. Metabolite radioprofile of a 72- to 120-hour pooled feces sample after a single oral dose of [^{14}C]-tivozanib to a representative subject (1.5 mg, ~160 µCi).



Urine

- Unchanged [^{14}C] tivozanib was not detected in the urine (**Figure 5**). Three major, unknown metabolites (M29, M35, and M40) were detected in urine samples and represented 0.764% to 10.3% of the radioactive dose in the analyzed samples

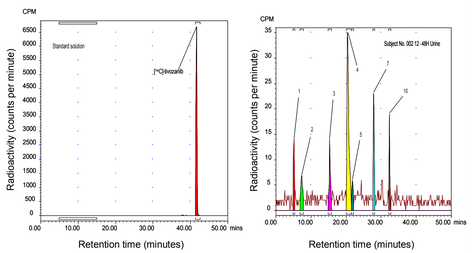
Safety

- AEs reported by more than one subject are presented in **Table 4**
- The most commonly reported AEs were Grade 1 gastrointestinal disorders, including mild diarrhea and upper abdominal pain
- There were no deaths or serious AEs in this study

Table 4. Adverse Events Occurring in More Than One Subject

Adverse Event	Number of Subjects (%)
Diarrhea	4 (50)
Headache	2 (25)

Figure 5. A) Chromatogram of [^{14}C] tivozanib standard alone. B) Absence of standard tivozanib peak in a representative subject pooled 12- to 48-hour eluate sample indicating absence of tivozanib in the urine.



A. Chromatogram of [^{14}C]-tivozanib standard alone.

B. Absence of standard tivozanib peak in representative patient pooled 12- to 48-hour eluate sample indicating absence of tivozanib in the urine.

Conclusions

- These results indicate that after an oral dose of 1.5 mg (~160 µCi) of [^{14}C]-tivozanib, the majority of circulating drug in the systemic circulation was unchanged [^{14}C]-tivozanib
- A mean of 79.3% of the dose was recovered in the feces
  - This indicates that elimination of [^{14}C]-tivozanib is primarily via the feces
  - The presence of metabolites in feces suggests a component of biliary excretion
- No unchanged [^{14}C]-tivozanib was found in the urine, indicating that tivozanib does not undergo renal excretion
- In this study, the mean $t_{1/2}$ of [^{14}C]-tivozanib was 89.3 hours
  - Results are consistent with those found in studies of tivozanib in oncology patients[3,6,8]
  - In spite of tivozanib's long $t_{1/2}$, a very high fraction of radiolabel was recovered
- Tivozanib does not display time-dependent kinetics, and therefore the results from this study can be extrapolated to the multiple-dose setting in oncology patients
- Tivozanib is currently being tested in a Phase III study in patients with RCC and Phase I/II studies in patients with other solid tumors

References

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