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Drug-Drug Interaction Study to Assess the Effect of Cytochrome P450 Inhibition and Induction on the Pharmacokinetics of the Novel Cereblon Modulator Avadomide (CC-122) in Healthy Adult Subjects

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Abstract

Avadomide (CC-122) is a novel immunomodulatory drug that binds to cereblon, a member of the Cullin 4-RING E3 ubiquitin ligase complex. Avadomide has multiple pharmacologic activities including potent immune modulation, antiangiogenic, antitumor, and antiproliferative activity and is being evaluated as an oncology treatment for hematologic malignancies and advanced solid tumors. In vitro study has indicated that cytochrome P450 (CYP) 3A and CYP1A2 appear to be the major enzymes involved in the oxidative metabolism of avadomide. The effects of CYP3A inhibition/induction and CYP1A2 inhibition on the pharmacokinetics of avadomide in healthy adult subjects were assessed in 3 parts of an open-label, nonrandomized, 2-period, single-sequence crossover study. Following a single oral dose of 3 mg, avadomide exposure when coadministered with the CYP1A2 inhibitor fluvoxamine was 154.81% and 107.59% of that when administered alone, for area under the plasma concentration-time curve from time 0 to infinity ($AUC_{0\text{-inf}}$) and maximum observed plasma concentration (C_{max}), respectively. Avadomide exposures, when coadministered with the CYP3A inhibitor itraconazole, were 100.0% and 93.64% of that when administered alone, for $AUC_{0\text{-inf}}$ and C_{max}, respectively. Avadomide exposures when coadministered with the CYP3A inducer rifampin were 62.83% and 88.17% of that when administered alone, for $AUC_{0\text{-inf}}$ and C_{max}, respectively. Avadomide was well tolerated when administered as a single oral dose of 3 mg alone or coadministered with fluvoxamine, itraconazole, or rifampin. These results should serve as the basis for avadomide dose recommendations when it is coadministered with strong CYP3A and CYP1A2 inhibitors and with rifampin.

Keywords

avadomide, CYP1A2, CYP3A, drug-drug interactions, immunomodulatory drug

Avadomide (CC-122) is a novel member of the immunomodulatory drug class that binds to cereblon, a member of the Cullin 4-RING E3 ubiquitin ligase complex.[1] This binding redirects ubiquitin ligase activities to several targets, promoting their degradation. Among these are Aiolos and Ikaros, hematopoietic transcriptional regulators critical to the function of normal and malignant lymphoid cells.[1] Avadomide has multiple pharmacologic activities including potent immune modulation, antiangiogenic, antitumor, and antiproliferative activity. Due to these potent activities, avadomide is being evaluated as an oncology treatment for non-Hodgkin lymphoma, including diffuse large B-cell lymphoma; chronic lymphocytic leukemia; multiple myeloma; and/or advanced solid tumors, including glioblastoma multiforme and hepatocellular carcinoma.[2]

The pharmacokinetics (PK) of avadomide was previously evaluated in patients with advanced solid tumors and hematologic malignancies as part of the first-in-human study.[2] Plasma avadomide exposure increased in a dose-dependent manner across the 0.5- to 3.5-mg dose range. The PK profile of avadomide was characterized by rapid absorption with half-life ranging from 7.7 to 27.9 hours, and the contribution of renal excretion to the elimination pathway was demonstrated based on the significant urinary recovery of avadomide

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(18% to 35% recovery of unchanged drug over 24 hours).[2] Healthy adult subjects receiving a single oral dose ranging from 3 to 15 mg avadomide showed a rapid absorption profile (time to maximum observed plasma concentration, t_{max} approximately 1 hour) and a mean half-life of 7.6 to 8.9 hours.[3] Single oral doses of up to 15 mg avadomide were well tolerated by the healthy subjects.[3]

The diseases for which avadomide is being developed can require multiple medications for treatment and supportive care; furthermore, these illnesses can manifest later in life when treatment is also required for aging-associated comorbidities. In vitro study using human liver microsomes implicated cytochrome P450 (CYP) 3A4/5 and CYP1A2 as the major enzymes involved in the oxidative metabolism of avadomide (data on file). Therefore, the objective of this study was to evaluate the effect of CYP3A inhibition and induction and CYP1A2 inhibition on avadomide PK in healthy adult subjects.

Methods

Study and Ethics

The study was approved by the institutional review board of the participating center and was conducted in accordance with the Declaration of Helsinki and the International Council for Harmonisation Guidelines for Good Clinical Practice. All subjects gave written informed consent before performance of any study-related procedures. CC-122-CP-006 (NCT03340662) was an open-label study to evaluate the effect of food (part 1) and CYP inhibition and induction (parts 2–4) on the PK of avadomide as formulated capsules in healthy adult subjects. Part 1 is not the focus of this article. Subjects participated in 1 part only, and 19 subjects each were enrolled in parts 2, 3, and 4, respectively.

Study Population

The main criteria for inclusion were being healthy male and female subjects of nonchildbearing potential who were between 18 and 55 years of age at the time of signing the informed consent form and who had a body mass index between 18 and 33 kg/m^2 at screening. Subjects must have been afebrile, with supine systolic blood pressure $\geq$90 and $\leq$140 mm Hg, supine diastolic blood pressure $\geq$50 and $\leq$90 mm Hg, pulse rate $\geq$40 and $\leq$110 beats per minute, and normal or clinically acceptable 12-lead ECGs at screening.

Subjects were excluded if they had used CYP3A and/or CYP1A2 inducers and/or inhibitors (including St. John wort)[4] within 30 days before the first dose administration. Wide interindividual differences in CYP1A2 expression and activity have been reported,[5] and these differences could be explained by both genetic and environmental factors.[6] Functional impacts of *CYP1A2* polymorphism on the enzyme activity have been investigated. The *CYP1A2*1F* allele (−163C>A in intron 1) is commonly identified with high and comparable frequencies across various populations[7] and confers higher enzyme inducibility of CYP1A2 in smokers.[8,9] *CYP1A2*1K* (−163C>A, −739T>G, and −729C>T in intron 1) is associated with lower CYP1A2 activity compared with the wild type in nonsmokers.[10] CYP1A2 more generally is highly inducible at both the mRNA and protein levels by a variety of chemicals, smoking, and several dietary factors through the aromatic hydrocarbon receptor.[11] To minimize the variability in CYP1A2 activity caused by genetic and environmental factors, *CYP1A2*1F* homozygotes, *CYP1A2*1K* heterozygotes and homozygotes, and smokers (>10 cigarettes per day, or the equivalent in other tobacco products [self-reported]) were excluded from this study. In addition, subjects who had a *CYP3A4*22* allele were excluded.

Study Design and Treatment

Part 2: CYP3A Inhibition. This was an open-label, nonrandomized, 2-period, single-sequence crossover study to evaluate the effect of coadministration of itraconazole (as oral solution), a strong CYP3A inhibitor, on avadomide PK in healthy adult subjects. Period 1 (avadomide only) spanned days –1 to 4, whereas period 2 (avadomide with itraconazole) subsequently spanned days –1 to 7 (Figure S1A). Eligible subjects checked in to the study center on day –1 of period 1 and remained domiciled at the study center through day 7 of period 2. All enrolled subjects received the same dosing regimen under fasted conditions: a single oral dose of 3 mg avadomide in the morning of day 1 of period 1; once daily (QD) oral dose of 200 mg itraconazole from days 1 to 3 of period 2; a single oral dose of 3 mg avadomide in the morning plus 1 oral dose of 200 mg itraconazole on day 4 of period 2; and oral doses of 200 mg itraconazole QD from days 5 to 6 of period 2. There was a washout period of 5 days between the dose on day 1 of period 1 and the first dose administration in period 2 (day 1 of period 2). Subjects were discharged from the study center on day 7 of period 2 on satisfactory safety review and on completion of study-related procedures. The itraconazole dose, dosage form, and duration used in this study were all based on the published data review of Liu et al.[12]

Part 3: CYP1A2 Inhibition. This was an open-label, nonrandomized, 2-period, single-sequence crossover study to evaluate the effect of coadministration of fluvoxamine, a strong CYP1A2 inhibitor, on avadomide PK in healthy adult subjects. Period 1 (avadomide only) spanned days –1 to 4; whereas period 2 (avadomide with fluvoxamine) subsequently spanned days –1 to

8 (Figure S1B). Eligible subjects checked in to the study center on day –1 of period 1 and remained domiciled there through day 8 of period 2. All enrolled subjects received the same dosing regimen under fasted conditions: a single oral dose of 3 mg avadomide in the morning of day 1 of period 1; twice daily (BID) oral doses of 50 mg fluvoxamine from days 1 to 4 of period 2; a single oral dose of 3 mg avadomide in the morning plus BID oral doses of 50 mg fluvoxamine on day 5 of period 2; and BID oral doses of 50 mg fluvoxamine on days 6 through 7 of period 2. There was a washout period of 5 days between the dose on day 1 of period 1 and first dose administration in period 2 (day 1 of period 2). Subjects were discharged from the study center on day 8 of period 2 on satisfactory safety review and completion of study-related procedures. The fluvoxamine dosage and duration that were employed were based on published experiences showing effects on CYP1A2 metabolism that are sufficiently large to interpret.[13,14]

Part 4: CYP3A4 Induction. This was an open-label, nonrandomized, 2-period, single-sequence crossover study to evaluate the effect of coadministration of rifampin, a strong CYP3A4 inducer, on avadomide PK in healthy adult subjects. Period 1 (avadomide only) spanned days –1 to 4; period 2 (avadomide with rifampin) subsequently spanned days –1 to 13 (Figure S1C). Eligible subjects checked in to the study center on day –1 of period 1 and remained domiciled there through day 13 of period 2. All enrolled subjects received the same dosing regimen under fasted conditions: a single oral dose of 3 mg avadomide in the morning of day 1 of period 1; an oral dose of 600 mg rifampin QD from days 1 through 9 of period 2; a single oral dose of 3 mg avadomide in the morning plus a single oral dose of 600 mg rifampin on day 10 of period 2; and an oral dose of 600 mg rifampin QD from days 11 through 12 of period 2. There was a washout period of 5 days between the dose on day 1 of period 1 and the first dose administration in period 2 (day 1 of period 2). Subjects were discharged from the study center on day 13 of period 2 on satisfactory safety review and completion of study-related procedures.

PK Data Collection

Plasma samples for measurement of avadomide were collected at predose and 0.5, 1, 2, 3, 4, 6, 8, 12, 24, 48, and 72 hours postdose of avadomide. Concentrations of avadomide in plasma were measured using a validated liquid chromatography tandem mass spectrometry assay with good accuracy (percentage relative error –5.67% to –1.67%) and precision (percentage coefficient of variation ≤6.80%) based on the quality control samples for the study. The lower limit of quantification (LLOQ) was 1 ng/mL, and the calibration range was 1–400 ng/mL. Plasma samples for measurement of itraconazole were collected at predose and 0.5, 1.5, 3, 6, 10, and 24 hours postdose of itraconazole. Concentrations of itraconazole in plasma were measured using a validated liquid chromatography tandem mass spectrometry assay with good accuracy (percentage relative error –1.32% to 5.33%) and precision (percentage coefficient of variation ≤5.28%) based on the quality control samples for the study. The LLOQ was 1 ng/mL, and the calibration range was 1–500 ng/mL. Itraconazole levels were measured to obtain an in-house PK dataset for this perpetrator compound.

Statistical Analyses of Pharmacokinetic Data

A total of 19 subjects were to be enrolled in each of parts 2, 3, and 4. The goal was to have approximately 48 subjects (16 subjects in each part) complete the study with sufficient evaluable plasma concentration data to adequately characterize PK. Assuming an intrasubject SD of 0.2 (obtained from prior studies with this compound [data on file]), the true ratio between treatments within (80% to 125%) and a no-effect boundary of (66.7% to 150%), 16 subjects were to provide 79% power to conclude that itraconazole, fluvoxamine, or rifampin has no effect on the PK of avadomide.

Noncompartmental analyses were conducted with Phoenix WinNonlin version 8.1 (Certara, Princeton, New Jersey) to estimate maximum observed plasma concentration (C_{max}), t_{max}, area under the plasma concentration-time curve (AUC) from time 0 to infinity ($AUC_{0\text{-}inf}$), AUC from time 0 to the last time point with a measurable plasma concentration ($AUC_{0\text{-}t}$), terminal elimination half-life ($t_{½}$), apparent clearance and apparent volume of distribution during the terminal phase.

To assess the effect of itraconazole, fluvoxamine, and rifampin on the PK of avadomide, an ANOVA was performed on the natural log–transformed $AUC_{0\text{-}t}$, $AUC_{0\text{-}inf}$, and C_{max}. The ANOVA model included treatment as fixed effect and subject as a random effect. The ratio of geometric means between the treatments ("coadministered drug + avadomide" versus "avadomide") and its 90%CIs were calculated. For t_{max}, Hodges-Lehman estimation was used for the median difference.

A postdose concentration below LLOQ was replaced with a value 50% of the LLOQ for the computation of geometric mean. If 50% or more of the values are below LLOQ at a time point, the descriptive statistics except for the maximum were not calculated.

Safety Assessment

Safety was monitored throughout the study. Safety evaluations included adverse event (AE) reporting,

Table 1. Demographic and Baseline Characteristics of Enrolled Subjects

Characteristics	Part 2 N = 19	Part 3 N = 19	Part 4 N = 19
Continuous variables, mean ± SD (range)			
Age (y)	32.8 ± 10.37 (19–53)	34.6 ± 8.00 (22–48)	38.2 ± 9.43 (26–52)
Height (cm)	174.44 ± 7.450 (161.3–192.6)	176.35 ± 5.201 (166.6–185.7)	175.42 ± 10.168 (152.6–194.1)
Weight (kg)	83.67 ± 14.602 (49.7–106.7)	88.16 ± 10.972 (73.3–109.1)	84.41 ± 12.289 (62.6–111.6)
BMI (kg/m^2)	27.48 ± 4.394 (18.5–32.6)	28.30 ± 2.889 (23.2–32.8)	27.38 ± 2.637 (19.8–30.9)
Categorical variables, N (%)			
Sex			
Male	18 (94.7)	18 (94.7)	18 (94.7)
Female	1 (5.3)	1 (5.3)	1 (5.3)
Race			
Black	8 (42.1)	12 (63.2)	10 (52.6)
White	10 (52.6)	7 (36.8)	9 (47.4)
Other	1 (5.3)	0	0
Ethnicity			
Hispanic or Latino	8 (42.1)	2 (10.5)	4 (21.1)
Not Hispanic or Latino	11 (57.9)	17 (89.5)	15 (78.9)

BMI indicates body mass index; N, number of subjects.

review of concomitant medications and procedures, physical examinations, 12-lead ECG, vital sign measurements, and clinical laboratory safety tests. All AEs were recorded by the investigator from the time the subject signed an informed consent form until at least 28 days after the last dose of the investigational product (IP), as well as those serious AEs made known to the investigator at any time thereafter that were suspected of being related to IP. All concomitant medications and procedures were reviewed and recorded from the time the subject signed the informed consent form until study completion.

Results

Demographics and Other Baseline Characteristics

A total of 57 subjects were enrolled: 19 subjects each in parts 2, 3, and 4, respectively. Fifty-five subjects completed the study, and 1 subject each in parts 3 and 4 discontinued from the study. Demographic and baseline characteristics data are summarized in Table 1. Overall, demographic characteristics were similar across study parts. There were 54 male subjects (94.7%) and 3 female subjects (5.3%) enrolled in the study. The mean age was 32.8–38.2 years (range 19–53 years), and the mean body mass index was 27.38–28.30 kg/m^2 (range 18.5–32.8 kg/m^2). The majority of subjects were white (26 subjects [45.6%]) or black (30 subjects [52.6%]). Fourteen subjects (24.6%) were Hispanic or Latino.

Effect of the CYP3A Inhibitor Itraconazole on Avadomide PK

Mean plasma avadomide concentration-versus-time profiles from a single oral dose of 3 mg avadomide when administered alone and when administered with the CYP3A inhibitor itraconazole were well characterized over the 72-hour postdose sampling interval (Figure 1 and Table 2: geometric mean ratio of $AUC_{0\text{-}t}$ to $AUC_{0\text{-}inf}$ was greater than 90%). The plasma PK parameters of avadomide when administered alone and when administered with itraconazole are summarized in Table 2, and the statistical analyses of PK parameters of avadomide are summarized in Table 3. The total plasma avadomide exposure ($AUC_{0\text{-}inf}$) was the same (707.8 h·ng/mL) when avadomide was administered alone and when administered with itraconazole. The plasma avadomide peak exposure (C_{max}) was similar when avadomide was administered alone and when administered with itraconazole (geometric means of 70.77 and 66.27 ng/mL, respectively). The median t_{max} was the same (1 hour) when avadomide was administered alone and when administered with itraconazole (Table 2). The total plasma exposure ($AUC_{0\text{-}inf}$) when administered with itraconazole was 100.0% (90%CI 94.79% to 105.50%) of that when administered alone. The plasma C_{max} when administered with itraconazole was 93.64% (90%CI 85.97% to 101.99%) of that when administered alone (Table 3).

Because exposures were so similar between periods 1 and 2, they were used to informally check the within-subject SD assumption described in the Materials and Methods. The value for this SD was measured as ~0.15, indicating that the assumed value of 0.2 was appropriate and somewhat conservative.

Mean plasma itraconazole concentration-versus-time profiles after 3 days of dosing 200 mg itraconazole oral solution were characterized over the 24-hour postdose sampling interval (Figure S2). Observed concentrations were in the range predicted to provide significant inhibition of CYP3A.[15]

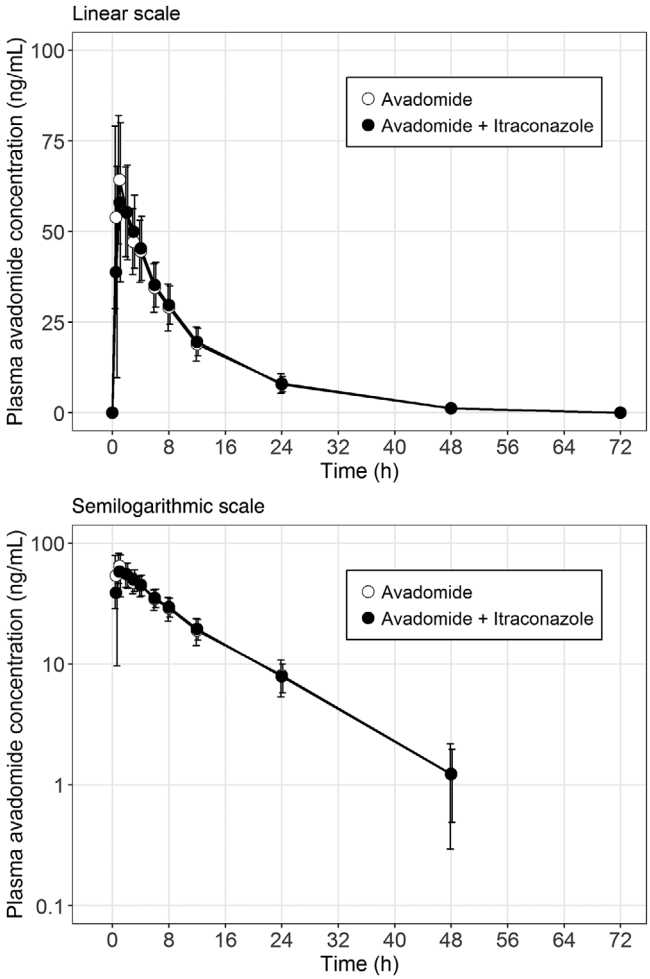

Figure 1. Mean (± SD) plasma avadomide concentration-time profile from a single oral dose of 3 mg avadomide when administered alone (open circles) and when administered with the CYP3A inhibitor itraconazole (closed circles), presented in linear (upper panel) and semilogarithmic (lower panel) scales.

Effect of CYP1A2 Inhibitor Fluvoxamine on Avadomide PK

Mean plasma avadomide concentration-versus-time profiles from a single oral dose of 3 mg avadomide when administered alone and when administered with the CYP1A2 inhibitor fluvoxamine were well characterized over the 72-hour postdose sampling interval (Figure 2 and Table 2; geometric mean ratio of $AUC_{0\text{-}t}$ to $AUC_{0\text{-}inf}$ was greater than 90%). The plasma PK parameters of avadomide when administered alone and when administered with fluvoxamine are summarized in Table 2, and the statistical analyses of PK parameters of avadomide are summarized in Table 4. The total plasma avadomide exposure ($AUC_{0\text{-}inf}$) was higher when avadomide was administered with fluvoxamine than that when administered alone (geometric means of 1095 and 718.3 h·ng/mL, respectively). The plasma avadomide C_{max} was similar when avadomide was administered with fluvoxamine as compared with that when administered alone (geometric means of 75.30 and 70.24 ng/mL, respectively). The median t_{max} was similar when avadomide was administered with fluvoxamine as compared with that when administered alone (0.79 and 0.50 hours, respectively) (Table 2). The total plasma exposure ($AUC_{0\text{-}inf}$) when administered with fluvoxamine was 154.81% (90%CI 145.09% to 165.17%) of that when administered alone. The plasma C_{max} when administered with fluvoxamine was 107.59% (90%CI: 96.61%–119.81%) of that when administered alone (Table 4).

Effect of CYP3A4 Inducer Rifampin on Avadomide PK

Mean plasma avadomide concentration-versus-time profiles from a single oral dose of 3 mg avadomide administered alone and when administered with the CYP3A4 inducer rifampin were well characterized over the 72-hour postdose sampling interval (Figure 3 and Table 2: geometric mean ratio of $AUC_{0\text{-}t}$ to $AUC_{0\text{-}inf}$ was greater than 90%). The plasma PK parameters of avadomide when administered alone and when

Table 2. Summary of Plasma Avadomide Pharmacokinetic Parameters by Treatment

	Geometric Mean (Geometric CV%)					
	Part 2		Part 3		Part 4	
PK Parameters	Avadomide Alone (N = 19)	Avadomide With Itraconazole (N = 19)	Avadomide Alone (N = 18)	Avadomide With Fluvoxamine (N = 18)	Avadomide Alone (N = 19)	Avadomide With Rifampin (N = 18)
$AUC_{0\text{-}t}$ (h·ng/mL)	675.4 (25.9)	679.1 (22.2)	675.2 (23.8)	1066 (19.5)	687.4 (28)	430.1 (20.1)
$AUC_{0\text{-}inf}$ (h·ng/mL)	707.8 (24.5)	707.8 (19.9)	718.3 (22)	1095 (19)	732.7 (25.3)	460.5 (21)
C_{max} (ng/mL)	70.77 (23.1)	66.27 (24.5)	70.24 (18.9)	75.30 (28)	74.77 (30.3)	65.99 (27.4)
t_{max} (h)	1 (0.5, 4)	1 (0.5, 4)	0.5 (0.5, 3)	0.79 (0.5, 3)	0.55 (0.5, 2)	0.53 (0.5, 2.62)
$t_{½}$ (h)	8.935 (17.5)	8.791 (18.2)	9.163 (13.6)	13.74 (11.1)	9.29 (18.2)	6.084 (13.4)
CL/F (L/h)	4.238 (24.5)	4.238 (19.9)	4.176 (22)	2.739 (19)	4.094 (25.3)	6.514 (21)
V_z/F (L)	54.67 (17.1)	53.78 (18.6)	55.25 (20.3)	54.27 (21.9)	54.95 (21.3)	57.29 (18.9)

$AUC_{0\text{-}inf}$ indicates area under the plasma concentration-time curve from time 0 to infinity; $AUC_{0\text{-}t}$, area under the plasma concentration-time curve from time 0 to the last time point with a measurable plasma concentration; CL/F, apparent clearance; C_{max}, maximum observed plasma concentration; CV%, percentage coefficient of variation; N, number of subjects; PK, pharmacokinetic; $t_{½}$, terminal elimination half-life; t_{max}, time to maximum observed plasma concentration; V_z/F, apparent volume of distribution during the terminal phase.
Median (min, max) data are presented.
N = 19.

Table 3. Statistical Analysis of Pharmacokinetic Parameters of Avadomide: AUCs and C_{max} of Avadomide When Administered Alone and With Itraconazole

Parameter	Treatment	N	Geometric LS Means	Treatment Comparison	Ratio of Geometric LS Means	90%CI of the Ratio	Intrasubject CV%
$AUC_{0\text{-}t}$ (h·ng/mL)	avadomide + itraconazole	19	679.1	avadomide + itraconazole/ avadomide	100.54	(94.54, 106.93)	11.0
	avadomide	19	675.4				
$AUC_{0\text{-}inf}$ (h·ng/mL)	avadomide + itraconazole	19	707.8	avadomide + itraconazole/ avadomide	100.00	(94.79, 105.50)	9.5
	avadomide	19	707.8				
C_{max} (ng/mL)	avadomide + itraconazole	19	66.27	avadomide + itraconazole/ avadomide	93.64	(85.97, 101.99)	15.3
	avadomide	19	70.77				

$AUC_{0\text{-}inf}$ indicates area under the plasma concentration-time curve from time 0 to infinity; $AUC_{0\text{-}t}$, area under the plasma concentration-time curve from time 0 to the last time point with a measurable plasma concentration; C_{max}, maximum observed plasma concentration; CV%, percentage coefficient of variation; LS, least squares; MSE, mean square error; N, number of subjects.
The estimates are from ANOVA with the natural log-transformed PK parameters as the dependent variable, treatment as fixed effects, and subject as a random effect. Intrasubject CV% = Square root of [exp(MSE of ANOVA) − 1] × 100.

administered with the CYP3A4 inducer rifampin are summarized in Table 2, and the statistical analyses of PK parameters of avadomide are summarized in Table 5. The total plasma avadomide exposure ($AUC_{0\text{-inf}}$) was lower when avadomide was administered with rifampin than that when it was administered alone (geometric means of 460.5 and 732.7 h·ng/mL, respectively). The plasma avadomide C_{max} was lower when avadomide was administered with rifampin than when it was administered alone (geometric means of 65.99 and 74.77 ng/mL, respectively). The median t_{max} was similar when avadomide was administered with rifampin as compared with that when administered alone (0.53 and 0.55 hours, respectively) (Table 2). The total plasma exposure ($AUC_{0\text{-inf}}$) when it was administered with rifampin was 62.83% (90%CI 59.41% to 66.45%) of that when it was administered alone. The plasma C_{max} when it was administered with rifampin was 88.17% (90%CI 80.10% to 97.07%) of that when administered alone (Table 5).

Safety

In part 2, 4 of 19 subjects (21.1%) reported at least 1 treatment-emergent AE (TEAE). Two subjects (10.5%) reported 2 TEAEs following administration of avadomide alone, and 2 subjects (10.5%) reported 2 TEAEs following administration of avadomide plus itraconazole. No subjects reported TEAEs after receiving itraconazole alone. None of the TEAEs reported were suspected of being related to the IP.

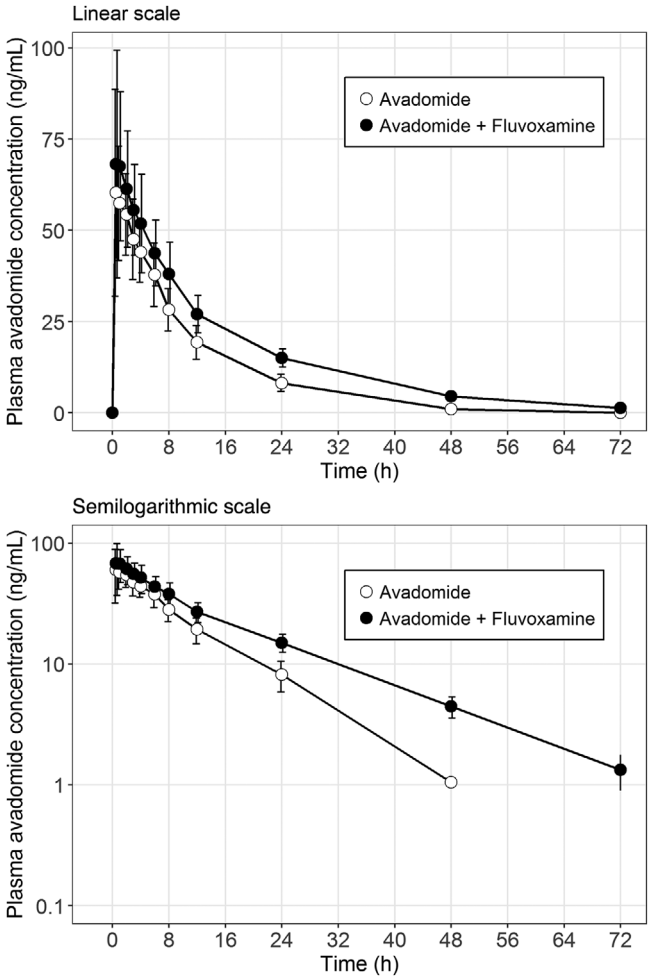

Figure 2. Mean (± SD) plasma avadomide concentration-time profile from a single oral dose of 3 mg avadomide when administered alone (open circles) and when administered with the CYP1A2 inhibitor fluvoxamine (closed circles), presented in linear (upper panel) and semilogarithmic (lower panel) scales.

In part 3, 12 of 19 subjects (63.2%) reported at least 1 TEAE. Seven subjects (38.9%) reported 9 TEAEs following administration of avadomide plus fluvoxamine, 6 subjects (31.6%) reported 11 TEAEs following administration of fluvoxamine alone, and 3 subjects (15.8%) reported 7 TEAEs following administration of avadomide alone. Treatment-emergent AEs suspected of being related to the IP were reported by 5 subjects (26.3%).

In part 4, 4 of 19 subjects (21.1%) reported at least 1 TEAE. Four subjects (22.2%) reported 5 TEAEs following administration of rifampin alone, and 1 subject (5.6%) reported 1 TEAE following administration of avadomide plus rifampin. No subjects reported TEAEs after receiving avadomide alone. Treatment-emergent AEs suspected of being related to the IP were reported by 1 subject (5.3%).

Overall, the most frequently reported TEAE was diarrhea (4 subjects, 7.0%), followed by infrequent bowel movements (3 subjects, 5.3%), and back pain (3 subjects, 5.3%). All other TEAEs were reported by 1 or 2 subjects each and had resolved by the end of the study. All TEAEs were mild in severity except for 1 moderate TEAE of vomiting experienced by 1 subject following administration of avadomide alone in part 3. The moderate TEAE of vomiting was considered related to the IP. One subject (part 3) discontinued the study due to a mild AE of syncope deemed by the investigator as possibly related to fluvoxamine. There were no serious AEs or deaths reported during the study.

One subject in part 3 experienced mild TEAEs of increased blood creatinine and proteinuria on day 8 of period 2 that the investigator considered clinically significant. Neither TEAE was suspected of being related to the IP. Blood creatinine and urine protein returned to within reference range on day 12, and both TEAEs were considered resolved. No other subject had a clinical laboratory safety result, vital sign measurement, 12-lead ECG result, or physical examination finding

Table 4. Statistical Analysis of Pharmacokinetic Parameters of Avadomide: AUCs and C_{max} of Avadomide When Administered Alone and With Fluvoxamine

Parameter	Treatment	N	Geometric LS Means	Treatment Comparison	Ratio of Geometric LS Means	90%CI of the Ratio	Intrasubject CV%
$AUC_{0\text{-}t}$ (h·ng/mL)	avadomide + fluvoxamine	18	1069	avadomide + fluvoxamine/ avadomide	160.35	(148.90, 172.69)	12.5
	avadomide	18	666.6				
$AUC_{0\text{-}inf}$ (h·ng/mL)	avadomide + fluvoxamine	18	1098	avadomide + fluvoxamine/ avadomide	154.81	(145.09, 165.17)	10.9
	avadomide	18	709.0				
C_{max} (ng/mL)	avadomide + fluvoxamine	18	75.57	avadomide + fluvoxamine/ avadomide	107.59	(96.61, 119.81)	18.9
	avadomide	19	70.24				

$AUC_{0\text{-}inf}$ indicates area under the plasma concentration-time curve from time 0 to infinity; $AUC_{0\text{-}t}$, area under the plasma concentration-time curve from time 0 to the last time point with a measurable plasma concentration; C_{max}, maximum observed plasma concentration; CV%, percentage coefficient of variation; LS, least squares; MSE, mean square error; N, number of subjects; PK, pharmacokinetic.

The estimates are from ANOVA with the natural log-transformed PK parameters as the dependent variable, treatment as fixed effects, and subject as a random effect. Intrasubject CV% = Square root of [exp(MSE of ANOVA) − 1] × 100.

that was considered clinically significant. There were no treatment-related trends in clinical laboratory safety test results, vital sign measurements, or 12-lead ECG results.

Discussion

The study was designed based on results of in vitro experiments, using pooled human liver microsomes treated with multiple reversible and irreversible chemical inhibitors and monoclonal antibodies, suggesting CYP3A4/5 and CYP1A2 to be the major isozymes involved in oxidative metabolism of avadomide. Effects on plasma avadomide concentrations of CYP3A inhibition, CYP1A2 inhibition, and CYP3A4 induction were evaluated in healthy subjects using a nonrandomized, single sequence, 2-period, crossover design in which avadomide PK was measured after administration alone and concomitantly with perpetrators. A single sequence, with avadomide being administered alone in the first period, was employed to minimize carryover effects and longer study duration associated with prolonged washout of the perpetrator compounds. The avadomide dose used in this study (single 3-mg oral dose) was appropriate from a safety perspective because single doses up to 15 mg were well tolerated in healthy subjects.[3] In addition, this dose level is directly relevant to potential clinical usage because it is tested in ongoing cancer studies.[2] Because the accumulation ratios are low in patients (ranging from 0.7 to 1.5),[2] PK findings using single doses of 3 mg plausibly apply to chronic dosing at similar levels.

To study effects of CYP3A inhibition, itraconazole oral solution was used. Itraconazole is accepted by the United States Food and Drug Administration as a strong in vivo CYP3A inhibitor and clinical perpetrator. The oral solution formulation was chosen for its good bioavailability under fasted conditions and its higher systemic exposure than that of the capsule formulation.[12] The itraconazole dosing regimen in this study, although not achieving steady state, provided sufficient degree and persistence of CYP3A inhibition to probe avadomide PK based both on published data review[12] and on the known plasma avadomide $t_{½}$ (without CYP inhibition) in healthy subjects (~8 hours).[3] Sustained and sufficient[15] plasma itraconazole concentrations over the 24 hours following multiple doses were confirmed (Figure S2). Avadomide exposures when administered with itraconazole were approximately 100.0% and 93.64%, for $AUC_{0\text{-}inf}$ and C_{max}, respectively, of those when it was administered alone. Given these findings, coadministration with strong CYP3A inhibitors is not expected to have clinically relevant effects on plasma avadomide exposures.

Fluvoxamine (oral tablet) was used as the CYP1A2 perpetrator because it is a strong inhibitor by Food and Drug Administration criteria, has good bioavailability under fasted conditions, and provides deep CYP1A2 inhibition after short dosing regimens.[14] The dose and duration of fluvoxamine in this study, although not quite achieving steady state, are considered to produce sufficient degree and persistence of CYP1A2 inhibition to probe avadomide PK based both on published data[13,14] and on plasma avadomide $t_{½}$ (without CYP inhibition) in healthy subjects.[3] In this study avadomide exposures when it was coadministered with fluvoxamine were 154.81% and 107.59%, for $AUC_{0\text{-}inf}$ and C_{max}, respectively, of those observed when it was administered alone. The larger impact on AUC than C_{max} suggests that fluvoxamine mainly contributes to the

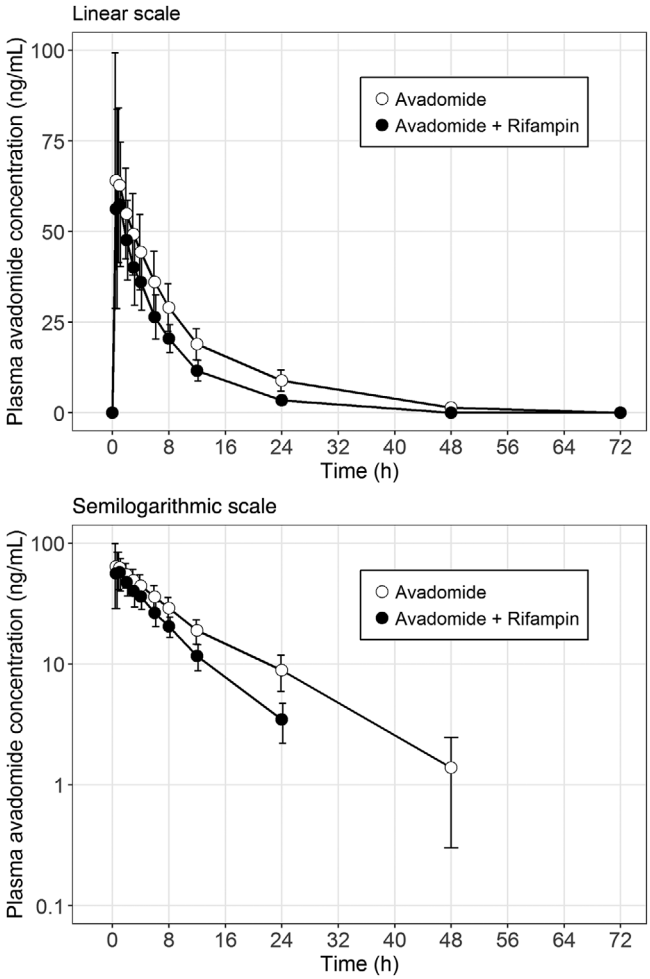

Figure 3. Mean (± SD) plasma avadomide concentration-time profile from a single oral dose of 3 mg avadomide when administered alone (open circles) and when administered with the CYP3A inducer rifampin (closed circles), presented in linear (upper panel) and semilogarithmic (lower panel) scales.

inhibition of avadomide clearance by hepatic CYP1A2 and, to a lesser extent, the inhibition of intestinal CYP1A2, supported by the finding that fluvoxamine coadministration prolonged avadomide $t_{½}$ by 50% and decreased apparent clearance by 34% with less pronounced increases in t_{max} and C_{max}.

Rifampin (oral capsule) was used as a CYP3A4 perpetrator because it is a well-documented strong CYP3A4 inducer.[16] Rifampin, when administered as a dose of 600 mg QD for 10 days, was anticipated to induce CYP3A4 and used to evaluate the effect of strong CYP3A4 induction on the PK of avadomide. Avadomide exposures when administered with the CYP3A4 inducer rifampin were 62.83% and 88.17%, for $AUC_{0\text{-inf}}$ and C_{max}, respectively, of those observed when administered alone. This contrasted with the essentially nil effect of the CYP3A inhibitor itraconazole. Similar findings of discordance between CYP3A inhibition and induction have been reported for several drugs, including ixazomib,[17] tivozanib,[18] and vandetanib[19]; this contrast has 1 of 2 possible main explanations. First, the induction of CYP3A-mediated metabolism by rifampin might cause a significant increase in clearance of avadomide, although the contribution of CYP3A to avadomide clearance is small at baseline. In the case of vandetabib such a regime was confirmed by direct measurement of large increases in plasma concentrations of CYP3A4-related metabolites under conditions of induction.[19] Second, rifampin could induce other pregnane X receptor-dependent drug-metabolizing enzymes and transporters.[20,21] Specifically, rifampin induces not only CYP3A4 expression but also intestinal P-glycoprotein (P-gp)[22] and CYP1A2 in vivo, supported by the finding that the rifampin produced a 15% increase in conversion of caffeine to paraxanthine mediated by CYP1A2 in healthy subjects.[23] Avadomide is a weak substrate for P-gp (data on file). The decrease in avadomide exposure by the coadministration of rifampin might thus be explained by mild-moderate induction of these other pharmacokinetically

Table 5. Statistical Analysis of Pharmacokinetic Parameters of Avadomide: AUCs and C_{max} of Avadomide When Administered Alone and With Rifampin

Parameter	Treatment	N	Geometric LS Means	Treatment Comparison	Ratio of Geometric LS Means	90%CI of the Ratio	Intrasubject CV%
$AUC_{0\text{-}t}$ (h·ng/mL)	avadomide + rifampin	18	428.5	avadomide + rifampin /avadomide	62.34	(58.20, 66.77)	11.9
	avadomide	19	687.4				
$AUC_{0\text{-}inf}$ (h·ng/mL)	avadomide + rifampin	18	460.3	avadomide + rifampin /avadomide	62.83	(59.41, 66.45)	9.7
	avadomide	19	732.7				
C_{max} (ng/mL)	avadomide + rifampin	18	65.93	avadomide + rifampin /avadomide	88.17	(80.10, 97.07)	16.8
	avadomide	19	74.77				

$AUC_{0\text{-}inf}$ indicates area under the plasma concentration-time curve from time 0 to infinity; $AUC_{0\text{-}t}$, area under the plasma concentration-time curve from time 0 to the last time point with a measurable plasma concentration; C_{max}, maximum observed plasma concentration; CV%, percentage coefficient of variation; LS, least squares; MSE, mean square error; N, number of subjects; PK, pharmacokinetic.

The estimates are from ANOVA with the natural log-transformed PK parameters as the dependent variable, treatment as fixed effects, and subject as a random effect. Intrasubject CV% = Square root of [exp(MSE of ANOVA) − 1] × 100.

important molecules. Indeed, the observed avadomide effects could also result from a combination of both processes. This seems to apply to ixazomib, whose PK was well reconciled by a physiologically based PK model incorporating a minor contribution of CYP3A to overall clearance, strong induction of CYP3A4, and moderate induction of intestinal P-gp.[17]

Safety assessment indicated that avadomide, administered as a single oral dose of 3 mg alone or coadministered with itraconazole, fluvoxamine, or rifampin, was well tolerated by the healthy subjects in this study. No new observed or suspected risks were suggested by the study results. Coadministration with perpetrators caused only a slight increase in avadomide C_{max}, and all observed avadomide concentrations fell within the range where little to no risk of QT prolongation was demonstrated.[3]

Avadomide is a novel member of the immunomodulatory drug class, which includes thalidomide, lenalidomide, pomalidomide, and structurally related compounds. These molecules have similar molecular structures; however, their often subtle chemical differences alter not only their substrate specificities[24] but also their PK profiles. For example, lenalidomide is not subject to significant CYP-based or conjugative metabolism and is instead eliminated mostly through renal excretion of the unchanged drug[25]; in contrast, pomalidomide is primarily metabolized by CYP1A2 and CYP3A, with a low fraction excreted in urine as unchanged drug.[26] Pomalidomide exposures when administered with the CYP3A inhibitor ketoconazole were 118.8% and 107.3%, for AUC and C_{max}, respectively, of that when administered alone.[27] Pomalidomide exposures when administered with the CYP3A4 inducer carbamazepine were 79.7% and 75.0%, for AUC and C_{max}, respectively, of that when administered alone.[27] These modest changes are not considered clinically relevant. Pomalidomide exposures when coadministered with the CYP1A2 inhibitor fluvoxamine were 225.1% and 123.7% of that when administered alone for AUC and C_{max}, respectively.[28]

Avadomide seems to have elimination and drug-drug interaction profiles intermediate between those of lenalidomide and pomalidomide. Similarly to the latter, avadomide is metabolized mainly by CYP3A and CYP1A2 in vitro (data on file), and inhibition of CYP1A2 but not CYP3A increased the exposure—the effect of CYP1A2 inhibition on exposure being somewhat smaller for avadomide than for pomalidomide (AUC, 154.81% versus 225.1% of that when administered alone). Somewhat similarly to lenalidomide, however, renal excretion plays a moderate role in avadomide elimination (18% to 35% urinary recovery over 24 hours).[2]

Conclusion

In summary, this study demonstrated that avadomide exposures, when administered with the CYP1A2 inhibitor fluvoxamine, were 154.81% and 107.59%, for $AUC_{0\text{-}inf}$ and C_{max}, respectively, of that when administered alone. Avadomide exposures when administered with the CYP3A inhibitor itraconazole were 100.0% and 93.64%, for $AUC_{0\text{-}inf}$ and C_{max}, respectively, of that when administered alone. Avadomide exposures when administered with the CYP3A4 inducer rifampin were 62.83% and 88.17%, for $AUC_{0\text{-}inf}$ and C_{max}, respectively, of that when administered alone. Generalization of the rifampin results to other medications may require further study of the mechanism by

which rifampin exerts its effect on avadomide levels; specifically, CYP3A4 induction alone may not explain the effects given the lack of effect of itraconazole, a strong CYP3A inhibitor. Avadomide, administered as a single oral dose of 3 mg alone or coadministered with fluvoxamine, itraconazole, or rifampin, was well tolerated in healthy subjects. These results should serve as the basis for avadomide dose recommendations when coadministered with strong CYP3A and CYP1A2 inhibitors and with rifampin.

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Data Sharing

Requests for access to data should be addressed to the corresponding author.

Disclosures

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References

1. Hagner PR, Man HW, Fontanillo C, et al. CC-122, a pleiotropic pathway modifier, mimics an interferon response and has antitumor activity in DLBCL. *Blood*. 2015;126(6):779-789.
2. Rasco DW, Papadopoulos KP, Pourdehnad M, et al. A first-in-human study of novel cereblon modulator avadomide (CC-122) in advanced malignancies. *Clin Cancer Res*. 2019;25(1):90-98.
3. Li Y, Carayannopoulos LN, Thomas M, Palmisano M, Zhou S. Exposure-response analysis to assess the concentration-QTc relationship of CC-122. *Clin Pharmacol*. 2016;8:117-125.
4. Indiana University School of Medicine. Drug Interactions Flockhart Table. https://drug-interactions.medicine.iu.edu/Main-Table.aspx. Accessed March 3, 2019.
5. Gunes A, Dahl ML. Variation in CYP1A2 activity and its clinical implications: influence of environmental factors and genetic polymorphisms. *Pharmacogenomics*. 2008;9(5):625-637.
6. Rasmussen BB, Brix TH, Kyvik KO, Brosen K. The interindividual differences in the 3-demthylation of caffeine alias CYP1A2 is determined by both genetic and environmental factors. *Pharmacogenetics*. 2002;12(6):473-478.
7. Zhou SF, Wang B, Yang LP, Liu JP. Structure, function, regulation and polymorphism and the clinical significance of human cytochrome P450 1A2. *Drug Metab Rev*. 2010;42(2):268-354.
8. Ghotbi R, Christensen M, Roh HK, Ingelman-Sundberg M, Aklillu E, Bertilsson L. Comparisons of CYP1A2 genetic polymorphisms, enzyme activity and the genotype-phenotype relationship in Swedes and Koreans. *Eur J Clin Pharmacol*. 2007;63(6):537-546.
9. Sachse C, Brockmoller J, Bauer S, Roots I. Functional significance of a C→A polymorphism in intron 1 of the cytochrome P450 CYP1A2 gene tested with caffeine. *Br J Clin Pharmacol*. 1999;47(4):445-449.
10. Aklillu E, Carrillo JA, Makonnen E, et al. Genetic polymorphism of CYP1A2 in Ethiopians affecting induction and expression: characterization of novel haplotypes with single-nucleotide polymorphisms in intron 1. *Mol Pharmacol*. 2003;64(3):659-669.
11. Ma Q, Lu AY. CYP1A induction and human risk assessment: an evolving tale of in vitro and in vivo studies. *Drug Metab Dispos*. 2007;35(7):1009-1016.
12. Liu L, Bello A, Dresser MJ, et al. Best practices for the use of itraconazole as a replacement for ketoconazole in drug-drug interaction studies. *J Clin Pharmacol*. 2016;56(2):143-151.
13. Culm-Merdek KE, von Moltke LL, Harmatz JS, Greenblatt DJ. Fluvoxamine impairs single-dose caffeine clearance without altering caffeine pharmacodynamics. *Br J Clin Pharmacol*. 2005;60(5):486-493.
14. Jeppesen U, Gram LF, Vistisen K, Loft S, Poulsen HE, Brosen K. Dose-dependent inhibition of CYP1A2, CYP2C19 and CYP2D6 by citalopram, fluoxetine, fluvoxamine and paroxetine. *Eur J Clin Pharmacol*. 1996;51(1):73-78.
15. Templeton IE, Thummel KE, Kharasch ED, et al. Contribution of itraconazole metabolites to inhibition of CYP3A4 in vivo. *Clin Pharmacol Ther*. 2008;83(1):77-85.
16. Liu Y, Zhou S, Wan Y, Wu A, Palmisano M. The impact of co-administration of ketoconazole and rifampicin on the pharmacokinetics of apremilast in healthy volunteers. *Br J Clin Pharmacol*. 2014;78(5):1050-1057.
17. Gupta N, Hanley MJ, Venkatakrishnan K, et al. Effects of strong CYP3A inhibition and induction on the pharmacokinetics of ixazomib, an oral proteasome inhibitor: results of drug-drug interaction studies in patients with advanced solid tumors or lymphoma and a physiologically based pharmacokinetic analysis. *J Clin Pharmacol*. 2018;58(2):180-192.
18. Cotreau MM, Siebers NM, Miller J, Strahs AL, Slichenmyer W. Effects of ketoconazole or rifampin on the pharmacokinetics of tivozanib hydrochloride, a vascular endothelial growth factor receptor tyrosine kinase inhibitor. *Clin Pharmacol Drug Dev*. 2015;4(2):137-142.
19. Martin P, Oliver S, Robertson J, Kennedy SJ, Read J, Duvauchelle T. Pharmacokinetic drug interactions with vandetanib during coadministration with rifampicin or itraconazole. *Drugs R D*. 2011;11(1):37-51.
20. Chen J, Raymond K. Roles of rifampicin in drug-drug interactions: underlying molecular mechanisms involving the nuclear pregnane X receptor. *Ann Clin Microbiol Antimicrob*. 2006;5:3.
21. Niemi M, Backman JT, Fromm MF, Neuvonen PJ, Kivisto KT. Pharmacokinetic interactions with rifampicin: clinical relevance. *Clin Pharmacokinet*. 2003;42(9):819-850.
22. Lutz JD, Kirby BJ, Wang L, et al. Cytochrome P450 3A induction predicts P-glycoprotein induction; part 1: establishing induction relationships using ascending dose r ifampin. *Clin Pharmacol Ther*. 2018;104(6):1182-1190.
23. Branch RA, Adedoyin A, Frye RF, Wilson JW, Romkes M. In vivo modulation of CYP enzymes by quinidine and rifampin. *Clin Pharmacol Ther*. 2000;68(4):401-411.
24. Kronke J, Fink EC, Hollenbach PW, et al. Lenalidomide induces ubiquitination and degradation of CK1α in del(5q) MDS. *Nature*. 2015;523(7559):183-188.
25. Chen N, Zhou S, Palmisano M. Clinical pharmacokinetics and pharmacodynamics of lenalidomide. *Clin Pharmacokinet*. 2017;56(2):139-152.

26. Hoffmann M, Kasserra C, Reyes J, et al. Absorption, metabolism and excretion of [^{14}C]pomalidomide in humans following oral administration. *Cancer Chemother Pharmacol*. 2013;71(2):489-501.
27. Kasserra C, Assaf M, Hoffmann M, et al. Pomalidomide: evaluation of cytochrome P450 and transporter-mediated drug-drug interaction potential in vitro and in healthy subjects. *J Clin Pharmacol*. 2015;55(2):168-178.
28. Li Y, Liu L, Wang X, et al. In vivo assessment of the effect of CYP1A2 inhibition and induction on pomalidomide pharmacokinetics in healthy subjects. *J Clin Pharmacol*. 2018;58(10):1295-1304.

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