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Published in:
Clinical Pharmacology & Therapeutics

DOI:
10.1002/cpt.1515

IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

Document Version
Publisher's PDF, also known as Version of record

Publication date:
2019

Link to publication in University of Groningen/UMCG research database

Citation for published version (APA):
Lubberman, F. J. E., Gelderblom, H., Hamberg, P., Vervenne, W. L., Mulder, S. F., Jansman, F. G. A., Colbers, A., van der Graaf, W. T. A., Burger, D. M., Luelmo, S., Moes, D. J. A. R., van Herpen, C. M. L., & van Erp, N. P. (2019). The Effect of Using Pazopanib With Food vs. Fasted on Pharmacokinetics, Patient Safety, and Preference (DIET Study). *Clinical Pharmacology & Therapeutics*, *106*(5), 1076-1082. https://doi.org/10.1002/cpt.1515

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The Effect of Using Pazopanib With Food vs. Fasted on Pharmacokinetics, Patient Safety, and Preference (DIET Study)

Floor J.E. Lubberman[1], Hans Gelderblom[2], Paul Hamberg[3], Walter L. Vervenne[4], Sasja F. Mulder[5], Frank G.A. Jansman[6,7], Angela Colbers[1], Winette T.A. van der Graaf[5], David M. Burger[1], Saskia Luelmo[2], Dirk Jan A.R. Moes[8], Carla M.L. van Herpen[5] and Nielka P. van Erp[1,*]

Pazopanib is taken fasted in a fixed oral daily dose of 800 mg. We hypothesized that ingesting pazopanib with food may improve patients' comfort and reduce gastrointestinal (GI) adverse events. Therefore, we investigated the bioequivalent dose of pazopanib when taken with food compared with 800 mg pazopanib taken fasted. In addition, we investigated the differences in GI toxicity, patient satisfaction, and patient's preference for either intake. The intake of 600 mg pazopanib with food resulted in a bioequivalent exposure and was preferred over a standard pazopanib dose without food. No differences were seen in GI toxicities under both intake regimens. Patients seem to be more positive about their feelings about side effects and satisfaction with their therapy when pazopanib was taken with food. Forty-one of the patients (68%) preferred the intake with a continental breakfast.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

☑ Pazopanib has a bioavailability of ~ 21% when ingested in a fasted state. When ingested with food, the solubility of pazopanib improves. Intake of pazopanib with a high-fat US Food and Drug Administration meal resulted in a twofold increase in maximum peak concentration and area under the concentration-time curve.

WHAT QUESTION DID THIS STUDY ADDRESS?

☑ Does a reduced yet bioequivalent pazopanib dose when ingested with a continental breakfast (CB) lead to a reduced occurrence of gastrointestinal toxicity and improve patients' treatment satisfaction?

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

☑ Our results show that the use of a 600 mg pazopanib dose taken with a CB is bioequivalent to 800 mg pazopanib taken in a fasted state. This is a more patient-friendly intake regimen and indicates improved patient satisfaction.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?

☑ The breakfasts used in our study are very much compatible with daily life in our outpatient setting. This could potentially contribute to drug adherence and total pazopanib treatment duration.

Pazopanib is approved for the treatment of metastatic renal cell carcinoma (mRCC) and soft tissue sarcoma (STS) at a fixed oral dose of 800 mg daily, taken fasted.[1,2] Pazopanib is extensively protein bound (>99%) and has a relatively long half-life of ~ 31 hours.[3] The elimination is predominantly via feces with renal elimination accounting for <4% of the administered dose.[4] Pazopanib is metabolized through CYP3A4 with CYP1A2 and CYP2C8 playing a minor role.[5] Pazopanib is the predominant component in the circulation.[4] Seven pazopanib metabolites have been identified. All of the metabolites represent <1% of the total pazopanib exposure. Therefore, they do not seem to play a significant role in the efficacy of pazopanib.[4,6]

Although pazopanib is generally well tolerated, gastrointestinal (GI) side effects, such as diarrhea (52%), nausea (26%), and vomiting (21%), commonly occur.[1,2] Intake with food has shown to improve the GI tolerability of other orally administered tyrosine

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Received February 15, 2019; accepted April 22, 2019. doi:10.1002/cpt.1515

kinase inhibitors (e.g., ceritinib and bosutinib).[7,8] When pazopanib is taken under fasted conditions, a modest bioavailability of ~ 21% is observed. This is caused by the lipophilic character of pazopanib. When exposed to more lipophilic conditions, such as after food intake, the solubility of pazopanib improves.[4] Intake of pazopanib with a high-fat US Food and Drug Administration meal resulted in a twofold increase in maximum peak concentration (C_{max}) and area under the concentration-time curve ($AUC_{0-24\,hours}$).[6] Therefore, Heath *et al.*[6] concluded that the bioavailability of pazopanib is significantly affected when coingested with food, resulting in the recommended intake of pazopanib on an empty stomach.

However, abstaining from food for several hours per day might have an impact on the patient's quality of life. On the contrary, daily intake of the US Food and Drug Administration meals is not compatible with a normal healthy lifestyle due to the high amount of calories and fat (e.g., 800–1,000 calories, of which 55–66 g is fat).[6] Intake with a standard continental breakfast (CB) could be an easy to implement and patient-friendly alternative. Hereto, the effect of a CB with less calories and fat on pazopanib bioavailability needs to be determined first.

Given the known safety profile of pazopanib, the known effect of food on its bioavailability, the observation that food improved the GI tolerability of other tyrosine kinase inhibitors, and the high cost related to pazopanib treatment; we wanted to investigate if a reduced yet bioequivalent pazopanib dose when concomitantly ingested with a CB could lead to a reduced occurrence of gastrointestinal toxicity (diarrhea and nausea), improve patients' treatment satisfaction, and reduce pazopanib drug costs.

RESULTS

For the pharmacokinetic (PK)-dose finding study (part 1, **Figure 1**), a total of 19 patients with either mRCC or STS using pazopanib were included between May 2014 and December 2015. They received 800 mg pazopanib o.d. in a fasted state during 2 weeks followed by 600 mg pazopanib o.d. taken with CB for another 2 weeks. Of these 19 patients, 2 patients did not complete the period of 4 weeks due to disease progression. One patient was treated with a reduced dose of 400 mg pazopanib due to previously experienced toxicity and did not meet the inclusion criteria of the study. Therefore, the PK analysis was performed in 16 patients. Of these 16 patients, 50% were men. Sixty-two percent of the patients were treated for mRCC (**Table 1**).

The geometric mean ratio (GMR), including their 95% confidence interval (CI) of the $AUC_{0-24\,hours}$, C_{max}, and trough plasma concentration (C_{trough}), were 821 mg*hour/L (CI 657–1,025),

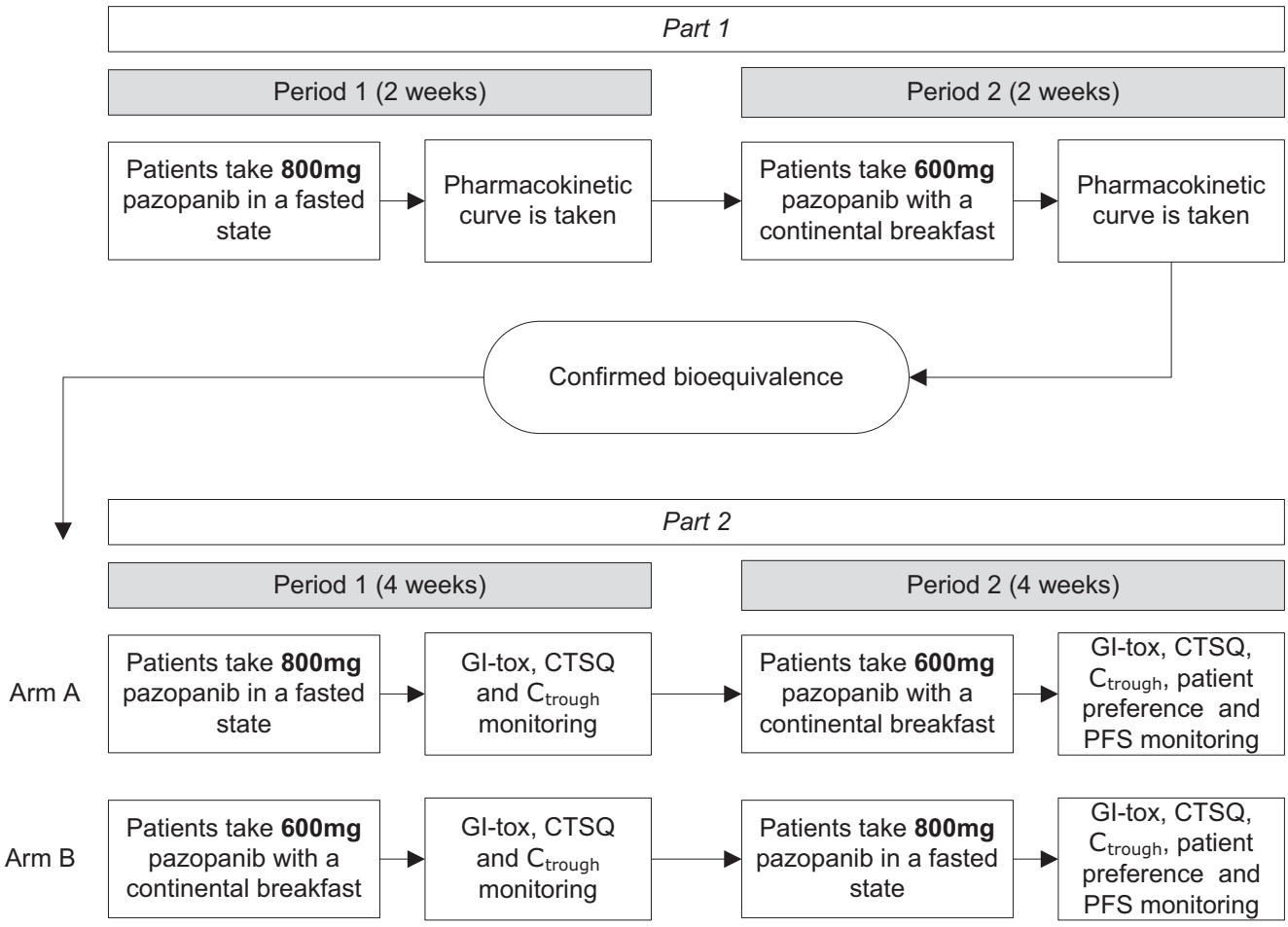

Figure 1 Study design. CTSQ, Cancer Therapy Satisfaction Questionnaire; C_{trough}, pazopanib trough level; GI-tox, gastrointestinal toxicity; PFS, progression-free survival.

Table 1 Patient characteristics at baseline

	Part 1		Part 2	
	No.	%	No.	%
Patients				
Age, year	16		60	
Median (range)	58 (35–77)		62 (28–85)	
Sex				
Female	8	50	16	27
Male	8	50	44	73
BMI, kg/m^2				
Median (range)	24 (21–30)		26 (19–52)	
ECOG performance status				
0	11	69	22	37
1	5	31	32	53
2	0		1	2
Unknown	0		5	8
Primary tumor				
Renal cell carcinoma	10	62	47	78
STS	6	38	12	20
Other	0	0	1	2

BMI, body mass index; ECOG, Eastern Cooperative Oncology Group; STS, soft tissue sarcoma.

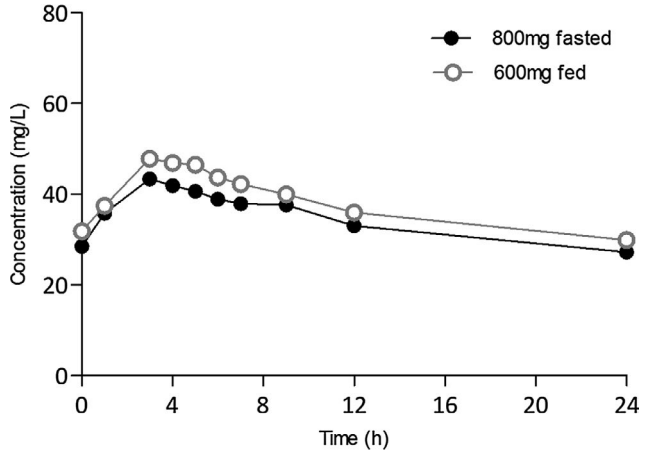

Figure 2 Concentration-time curve of the area under the concentration-time curve$_{0–24\ hours}$, maximum peak concentration, and pazopanib trough level of 800 mg pazopanib ingested in a fasted state and 600 mg pazopanib ingested with a continental breakfast.

44.8 mg/L (CI 36.5–55.2), and 27.2 mg/L (CI 21.4–34.7) when 800 mg pazopanib was taken in a fasted state compared with 895 mg*hour/L (CI 698–1,148), 50.2 mg/L (CI 38.8–64.8), and 29.9 mg/L (CI 22.9–39.0) when a reduced dose of 600 mg pazopanib was taken with a CB (**Table 2, Figures 2 and 3**). Interpatient variability (coefficient of variance (CV)) for AUC$_{0–24\ hours}$, C_{max}, and C_{trough} was 36%, 33%, and 42% when ingested fasted and 38%, 39%, and 42% when the reduced dose was taken with a CB, respectively. At steady state, the 600 mg pazopanib taken with food showed a bioequivalent exposure for AUC$_{0–24\ hours}$ with a GMR of 1.09 (90% CI 1.02–1.17), for C_{max} with a GMR of 1.12 (90% CI 1.04–1.20), and C_{trough} with a GMR of 1.10 (90% CI 1.02–1.18) when compared with the 800 mg fasted intake. Between February 2016 and July 2018, a total of 78 patients were enrolled and underwent randomization, with 38 patients randomly assigned to start with 800 mg fasted (arm A) and 40 to start with 600 mg with a CB (arm B; part 2, **Figure 1**). Three patients never started pazopanib treatment, one patient withdrew consent. Fourteen patients discontinued study participation due to disease progression ($n = 2$), GI toxicity ($n = 2$), and other adverse events ($n = 10$). Of the 14 patients who discontinued study participation, 11 patients stopped in the first period of 4 weeks. Nine patients stopped while using the 800 mg fasted regimen. Therefore, 60 patients were included in the analysis of which 28 patients were treated in arm A and 32 in arm B. A total of 57 patients completed their diaries during both treatment periods and were included in the GI toxicity analysis. With regard to the analysis of the questionnaire, the expectation of therapy (ET) analysis was based on 56 patients and both the feelings about side effects (FSEs) and satisfaction with treatment (SWT) analysis were based on 55 of the 60 patients. Pazopanib trough level samples after both treatment periods were retrieved in 59 patients. All 60 patients were included in the exploratory progression-free survival (PFS) analysis. The baseline characteristics of part 2 of the study are shown in **Table 1**. The majority of the patients were men (73%), and the median age was 62 years (range 28–85 years).

The mean number of stools per day was 1.70 when pazopanib was ingested with 800 mg fasted compared with 1.66 stools per day when taken with food ($P = 0.61$). In addition, no difference was seen in frequency of vomiting per day ($P = 0.94$) and nausea ($P = 0.66$). An overview of the scored GI toxicities is shown in **Table 3**. During study participation, no grade 4 adverse events occurred. In both intake regimens, six grade 3 adverse events occurred

Table 2 PK parameters of pazopanib at steady state

	800 mg fasted	600 mg fed
AUC$_{0–24\ hours}$, mg/hour/L, GMR (%CV, range)	821 (36, 292–1,516)	895 (38, 249–1,727)
C_{max}, mg/L, GMR (%CV, range)	44.8 (33, 17.4–74.6)	50.2 (39, 13.8–90.0)
C_{trough}, mg/L, GMR (%CV, range)	27.2 (42, 9.0–57.6)	29.9 (42, 7.8–60.7)
T_{max}, hours, median (range)	3.0 (1.0–5.1)	4.0 (3.0–9.1)

%CV, percentage of coefficient of variation defined by (standard deviation/mean) × 100; AUC$_{0–24\ hours}$, area under the concentration time curve 0 to 24 hours; C_{max}, maximum observed plasma concentration; C_{trough}, plasma concentration at $t = 24$ hours; GMR, geometric mean ratio; PK, pharmacokinetic; T_{max}, time to maximum plasma concentration.

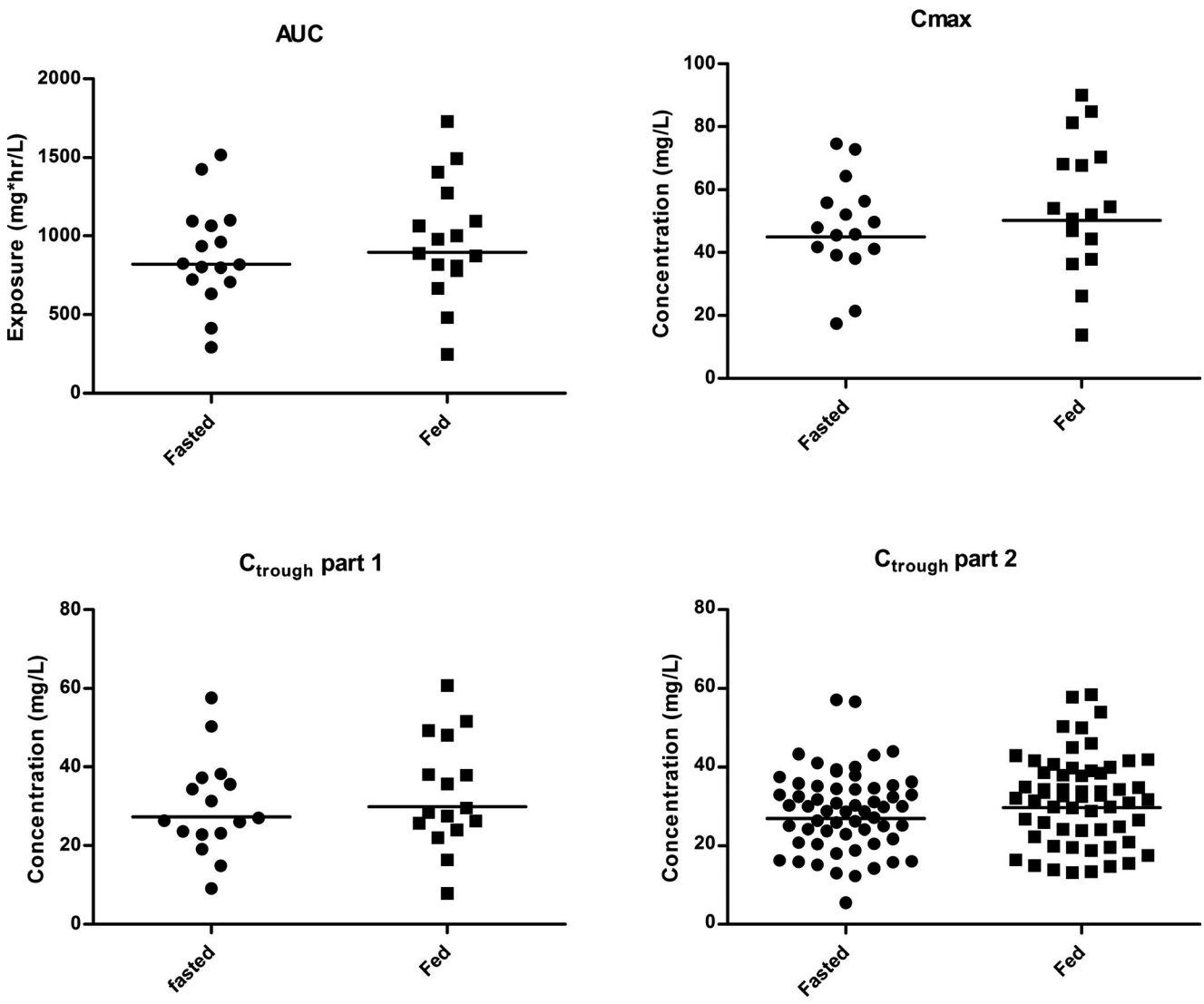

Figure 3 Plot of the individual $AUC_{0–24\ hours}$, C_{max}, and C_{trough} of 800 mg pazopanib ingested in a fasted state and 600 mg pazopanib ingested with a continental breakfast of part 1 and C_{trough} for part 2 of the study. $AUC_{0–24\ hours}$, area under the concentration-time curve 0 to 24 hours; C_{max}, maximum peak concentration; C_{trough}, pazopanib trough level.

Table 3 Adverse events pazopanib and CTSQ

	800 mg fasted	600 mg fed	*P* value
Number of stools per day, mean (%CV)	1.70 (47)	1.66 (38)	0.61
Times vomited per day, mean (%CV)	0.02 (254)	0.02 (314)	0.94
Nausea, mean (%CV)	0.15 (194)	0.14 (197)	0.66
ET, mean (%CV)	54.0 (30)	52.0 (31)	0.47
FSE, mean (%CV)	68.2 (30)	72.3 (22)	0.09
SWT, mean (%CV)	82.0 (15)	84.7 (14)	0.06

CTSQ, Cancer Therapy Satisfaction Questionnaire; CV, variation coefficient; ET, expectations of Therapy; FSE, feelings about side effects; SWT, satisfaction with therapy.

of which hypertension was the most dominant (in three patients under both intake regimens). The other adverse events were fatigue, hair discoloration, pain, and pneumonia.

After the trial ended, patients could choose whether they wanted to continue using 600 mg with a CB or if they wanted to return to 800 mg fasted, not having the knowledge on drug exposure. Forty-one of the 60 patients (68%) preferred to continue with 600 mg taken with breakfast, 15 patients (25%) preferred the 800 mg taken in a fasted state, and 4 (7%) patients had no preference.

With regard to patient comfort, patients seemed to be more positive about the intake of 600 mg pazopanib with a CB compared with 800 mg fasted with an FSE score of 72.3 (95% CI 68.1–76.5) vs. 68.2 (95% CI 62.7–73.6; $P = 0.09$), and an SWT score of 84.7 (95% CI 81.4–87.9) vs. 81.9 (95% CI 78.7–85.2; $P = 0.06$). The ET scores were 54.0 (95% CI 49.7–58.2) vs. 52.0 (95% CI 47.6–56.3; $P = 0.47$) when 800 mg pazopanib was ingested in a fasted state vs. 600 mg with food. This indicates an improved treatment satisfaction when 600 mg of pazopanib was taken with food (**Table 3**).

Pazopanib trough levels were, on average, 10% higher in the 600 mg fed regimen compared with the 800 mg fasted regimen

(29.7 mg/mL; 95% CI 26.8–32.9; percentage of coefficient of variation (%CV) 35.2) vs. 26.9 mg/L (95% CI 24.2–29.9; %CV 35.2). Still, the GMR, including the 90% CI, remained between the thresholds for bioequivalence (1.10 (90% CI 1.02–1.20)), confirming similar exposure between the two intake regimens.

After the study ended and patients continued with their preferred intake regimen, an exploratory PFS analysis was performed. We noted no significant differences in the PFS in the group of patients who continued therapy with the fed vs. fasted intake regimen (hazard ratio (HR) 1.14; 95% CI 0.54–2.43; $P = 0.70$; **Figure S1**), no differences were seen when the analysis was split per tumor type. The HR of mRCC was 1.56, 95% CI 0.59–4.08, $P = 0.37$, and the STS HR was 0.84, 95% CI 0.22–3.18, $P = 0.80$.

DISCUSSION

This study has demonstrated that by simple food intervention the daily dose of pazopanib can be reduced with 25% while maintaining a bioequivalent exposure compared with the recommended intake without food. The frequency and severity of gastrointestinal side effects (diarrhea, vomiting, and nausea) were comparable between the two intake regimens. However, almost three times more patients preferred to take the reduced pazopanib dose of 600 mg with food. Furthermore, the Cancer Therapy Satisfaction Questionnaire (CTSQ) indicated an improved patient satisfaction. Finally, although exploratory, no difference in treatment efficacy, as defined by PFS, was seen between both intake regimens.

To the best of our knowledge, this is the first study to investigate the effect of a reduced dose of pazopanib when taken with a CB on the steady-state exposure, GI toxicities, and preference in patients with cancer. For all recently approved oral oncolytic agents, the effect of food is being studied as part of the drug's registration process. Many of these oral oncolytic agents have a proven food effect and an alternative dosing strategy could be interesting to investigate.[9] However, only two other oncolytic agents with an alternative dosing strategy combined with food has been studied (e.g., abiraterone and ceritinib).[7,10] Even more, the bioequivalence study performed on the reduced dose of ceritinib with a meal resulted in an adjustment of the drug's registration label even before the safety data were known.[11] Our study aimed to complement the bioequivalent results with GI-toxicity data and patient preference, which results in a more complete understanding of the advantages of the altered intake regimen in patients with cancer.

In part 1 of this study, the mean trough levels of the reduced dose taken with food increased by ~ 10%. Nevertheless, the GMRs remained within the boundaries for bioequivalence. The bioequivalent exposure of the 600 mg with the CB regimen was consolidated in the larger group in part 2 of this study. According to the study by Suttle *et al.* and confirmed by Verheijen *et al.*, pazopanib efficacy in patients with mRCC is correlated with trough levels above 20.5 mg/L.[12,13] The mean trough levels in both phases were well above this threshold, indicating that patients received adequate treatment under both intake regimens.

Notably, the occurrence of GI toxicity in both study arms is considerably lower when compared with the earlier performed phase II and III trials.[1,2,14] In these trials, adverse events are scored during the whole treatment period. We, on the contrary, only monitored the adverse events for a relatively short period of 4 weeks under both intake regimens. In addition, patients in our clinic are thoroughly informed about the expected adverse events. This might influence patient expectations of the nausea adverse events resulting in lower Common Terminology Criteria for Adverse Events scores. Furthermore, patients who experienced treatment limiting toxicity before day 56 were excluded from the study and replaced by a new patient. The treatment-limiting toxicity occurred more often in patients on the 800 mg fasted regimen. When these patients were replaced, an inclusion bias was introduced because patients who experienced few adverse events remained in the study and were included in the analysis. However, the higher occurrence of treatment-limiting toxicity in the 800 mg fasted regimen emphasizes that 600 mg taken with a CB is better tolerated.

Pazopanib is registered at a fixed dose of 800 mg taken on an empty stomach. The fasted intake of drugs interferes with the normal daily life of patients. Reports on adherence and persistence among patients with cancer shows that adherence ranges from 16–100%.[15] Patients using pazopanib with food showed to be more satisfied with the treatment. Therefore, taking pazopanib with food could potentially contribute to drug adherence and total pazopanib treatment duration.

As mentioned, Heath *et al.*[6] showed an increase in $AUC_{0-24\ hours}$ of 2.3 when pazopanib was taken with a high-fat meal and an increase of 1.9 when ingested with a low-fat meal. Based on these results, a twofold increase was expected because the total amount of fat in our breakfast was higher than the amounts of fat in the low-fat meal of Heath *et al.*[6] However, our study revealed that only a 25% dose reduction of pazopanib with a CB resulted in bioequivalent exposure compared with ingestion in a fasted state. Probably the relation between the amount of fat present in the food and the bioavailability of pazopanib is not as straightforward as expected on forehand. Other factors, such as formation of digestive juices, increased volume of gastrointestinal contents, or the increased residence time in the gastrointestinal tract, may play an important role in pazopanib absorption. The exact mechanisms responsible for pazopanib absorption needs to be evaluated.

The breakfasts used in our study were compatible with daily life in the outpatient setting in the Netherlands. However, they could be different from breakfasts regularly used in other countries, which might affect the absorption of pazopanib. By using different types of breakfasts containing equal amount of fat and calories compared with the breakfasts used in this study, extrapolation of our results and implementation of a dose reduction of 25% could be safely done. Nevertheless, when by mistake the reduced dose is ingested without food a reduced efficacy can occur. On the other hand, ingesting a normal dose with food potentially increases toxicity. It is, therefore, important that patients should be well-informed about their drug intake regimen and the plasma concentration of pazopanib should be monitored in order to assure an adequate intake and exposure.

The alternative dosing regimen of taking 600 mg with a CB can be used instead of 800 mg taken fasted. Due to the saturated absorption and, therefore, nonlinear PK of pazopanib, the effect of food on lower dosages of pazopanib is unknown and should be

further investigated. Based on the results of this study, no dose advise can be given when other dosage of pazopanib are given.

Often, an increase in interpatient variability (CV) is used as an argument to advise for the fasted intake of oral medication, because fasted intake is easily standardized. In this study, we showed that interpatient variability remained the same during both intake regimens, indicating that ingesting pazopanib with food does not increase variability in pazopanib exposure.

Assuming the price of the 200 mg tablets is lower than the price of a 400 mg tablet, reducing the pazopanib daily dose by 25% for all patients significantly impacts treatment costs. Considering the average PFS of 9.2 months for mRCC, the total drug cost for pazopanib treatment is ~ $34,000 per patient in the Netherlands.[2] A 25% dose reduction to 600 mg ingested with a CB results in a savings of ~ $8,500 per patient with mRCC. For STS with a median PFS of 4.2 months, the savings would be ~ $3,800 per patient.

In conclusion, the use of a 600 mg pazopanib dose taken with a CB is bioequivalent to 800 mg pazopanib taken in a fasted state. This is a more patient-friendly intake regimen and positively affects patient's satisfaction.

METHODS

Study design and procedures

This study was conducted in two parts. First, a PK study was performed to establish the bioequivalent dose of pazopanib when ingested with a CB (part 1). This part was designed as an open-label, crossover, multicenter, phase I study conducted in two centers in the Netherlands (Radboudumc (Nijmegen) and Leiden University Medical Center (Leiden); **Figure 1**).

Because the effect of a CB on pazopanib exposure was uncertain and the study was conducted in patients with cancer, a lead-in phase in three patients was introduced. Based on the data of Heath *et al.*,[6] a twofold increase in pazopanib exposure by a food intervention was presumed. Initially, we conservatively gave 600 mg pazopanib with food to prevent underdosing. The results of the first three patients were analyzed and evaluated before continuation. If the 25% reduced dose ingested with food in the lead-in phase seemed to be bioequivalent with regard to $AUC_{0-24\ hours}$, C_{max} compared with the 800 mg taken in fasted state, the next 13 patients would be exposed to the 25% dose reduction with food. When the 25% dose reducing strategy in the lead-in phase led to higher $AUC_{0-24\ hours}$ and C_{max}, a 50% dose reduction (i.e., 400 mg) would be tested for bioequivalence in 16 new patients.

After the bioequivalent dose was determined, part 2 of the study was initiated. Part 2 was performed to determine whether the intake of pazopanib with food resulted in a decrease in GI toxicities. This was an open-label, randomized, crossover, multicenter study at four hospitals in the Netherlands (Radboudumc (Nijmegen), Leiden University Medical Centre (Leiden), Franciscus Gasthuis & Vlietland (Rotterdam), and Deventer Hospital (Deventer); **Figure 1**). The study protocol was approved by the institutional ethics committee Arnhem-Nijmegen (Nijmegen) and was compliant with the Declaration of Helsinki. All patients gave written informed consent before entering the study. The study was registered at ClinicalTrials.gov, NCT02138526.

Patients enrolled in the first part of the study received 800 mg pazopanib taken fasted followed by one of the standardized continental breakfasts (**Table S1**) taken 1 hour later for a period of 2 weeks. Subsequently, patients switched to 600 mg pazopanib daily (25% dose reduction) in combination with one of the standardized CBs for 2 weeks. After both treatment periods, the PK of pazopanib was assessed. A decrease of 25% was a pragmatic choice due to tablet formulation of 200 mg.

After the bioequivalent dose with food was determined, part 2 of the study was conducted. Patients were randomized to receive 800 mg pazopanib in a fasted state for 1 month, after which they switched to receive 600 mg pazopanib with a CB for the next month (arm A) or vice versa (arm B; **Figure 1**). Compliance with pazopanib, prandial conditions, and the occurrence of GI toxicities were confirmed through patient diaries. After each treatment period, a pazopanib plasma trough level (e.g., 24 hours after pazopanib intake) was collected, and patients were asked to complete the CTSQ. In this questionnaire, patients' FSE, ET, and their SWT were assessed.[16,17] At the end of the study (day 56), patients were asked whether they preferred to continue treatment with 800 mg pazopanib taken in a fasted state or the bioequivalent dose of 600 mg taken with a CB.

In the event of a patient developing tumor progression or toxicity resulting in dose reduction or terminating pazopanib treatment during the trial, the patient was dropped from the study and was replaced by a new eligible patient.

The CBs were composed by a dietician from Radboudumc and designed to be similar to the breakfasts our patients normally would take. All proposed breakfasts contained the same amount of fat (9–10 g). The total amount of calories, proteins, and carbohydrates differed per breakfast, ranging from, respectively, 160–320 calories, 5–11 g, and 15–50 g (**Table 1**). Patients could choose which breakfast they used (**Table S2**).

Eligibility

Adult patients (age ≥ 18 years) were eligible if they received 800 mg pazopanib o.d. (both treatment-naive and patients on treatment) with an Eastern Cooperative Oncology Group performance status of 0–2. The use of proton pump inhibitors was allowed when the proton pump inhibitor was used at the same time throughout the study, which was standardized at 1 hour after pazopanib intake. The use of other substances known or likely to alter Cytochrome P 3A4 metabolism were prohibited during this study. Patients with gastrointestinal abnormalities that could influence the absorption of pazopanib were excluded.

PK

In part 1, blood samples for describing plasma concentration time curve of pazopanib were collected over 24 hours after reaching steady-state PK. After the first period (day 14) and the second period (day 28), the following scheduled time points were obtained: 0, 1, 3, 4, 5, 6, 7, 9, 12, and 24 hours after pazopanib intake.

Trough PK samples were collected in part 2 of the study before the dose on the last day of each treatment period (e.g., days 28 and 56). Pazopanib plasma concentrations were measured using a validated liquid chromatography tandem mass spectrometry method with a lower limit of quantification of 1 mg/L.[18] PK parameters were calculated by using the standard noncompartmental method with Phoenix WinNonlin 6.3 (Certera, Princeton, NJ) and included the pazopanib $AUC_{0-24\ hours}$, C_{max}, and C_{trough}.

Statistics

Based on an interpatient CV of 27.3%, an intrapatient CV of 24.7%, and a reference ratio of 1, a sample size of 16 patients was required for a power of 80%, a two-sided significance level of 0.05 and a CV of 20% on the log-transformed data.[19,20] A bioequivalent dose was assumed when the GMR fed/fasted, including the 90% CI of the $AUC_{0-24\ hours}$, C_{max}, and C_{trough} of pazopanib were within the range of 0.8 and 1.25.

In part 2 of the study, a sample size of 60 patients was needed to show a difference in occurrence of GI toxicities with a power of 80%, a two-sided significance level of 0.05 and a CV of 20%. This was based on an expected decrease in GI toxicities of 33%, reported by 60% of the patients treated with pazopanib.

The differences in GI toxicities was analyzed according to Altman *et al.*[21] to correct for a possible period effect. The CTSQs are scored

following the guideline provided by Abetz *et al.*[17] A nonparametric Mann–Whitney *U*-test was performed to compare the CTSQ scores. After the study treatment ended, the Kaplan–Meier approach was used to estimate PFS rates, and the stratified log rank test was performed to compare the PFS between the two intake regimens of patients who continued pazopanib treatment.

SUPPORTING INFORMATION

Supplementary information accompanies this paper on the *Clinical Pharmacology & Therapeutics* website (www.cpt-journal.com).

Figure S1. Kaplan–Meier progression-free survival analysis after treatment with pazopanib 800 mg in a fasted state and 600 mg taken with a continental breakfast. HR, hazard ratio.
Table S1. Breakfast composition.
Table S2. Cancer Therapy Satisfaction Questionnaire.

ACKNOWLEDGMENTS

The authors thank patients and their families, all investigators, research nurses M. den Hollander, S. Van Broekhoven, M. Papa, E. Ten Berge, E. Veurink, W. Rutten, M. Kuiperij, and A. Smits-van de Camp, and dietician Heidi Zweers who designed the breakfasts used in the study, and "Betaalbaar Beter" for the financial support.

FUNDING

Part of the study was sponsored by the health insurance company Stichting Volksgezondheidszorg within the program "Betaalbaar Beter."

CONFLICT OF INTEREST

C.vH. received grants from AstraZeneca, Bristol Meyer Squibb, Merck Sharp and Dohme, Merck, Ipsen, and Sanofi. W.vdG. received a grant from Novartis. N.vE. received grants from Novartis, Astellas, AstraZeneca, Bristol-Meyers Squibb, Gilead, Ipsen, Janssen, Pfizer, and Roche. All other authors declared no competing interests in relation to this work.

AUTHOR CONTRIBUTIONS

All authors wrote the manuscript. F.L., N.vE., C.vH., H.G., W.vdG., D.B., F.J., and A.C. designed the research. C.vH., H.G., S.L., S.M., W.vdG., P.H., and W.V. performed the research. F.L., D.J.M., N.vE., and A.C. analyzed the data. D.B. and F.J. contributed new reagents/analytical tools.

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1. van der Graaf, W.T. *et al.* Pazopanib for metastatic soft-tissue sarcoma (PALETTE): a randomised, double-blind, placebo-controlled phase 3 trial. *Lancet* **379**, 1879–1886 (2012).
2. Sternberg, C.N. *et al.* Pazopanib in locally advanced or metastatic renal cell carcinoma: results of a randomized phase III trial. *J. Clin. Oncol.* **28**, 1061–1068 (2010).
3. Hurwitz, H.I. *et al.* Phase I trial of pazopanib in patients with advanced cancer. *Clin. Cancer Res.* **15**, 4220–4227 (2009).
4. Deng, Y. *et al.* Bioavailability, metabolism and disposition of oral pazopanib in patients with advanced cancer. *Xenobiotica* **43**, 443–453 (2013).
5. Tan, A.R. *et al.* Effects of ketoconazole and esomeprazole on the pharmacokinetics of pazopanib in patients with solid tumors. *Cancer Chemother. Pharmacol.* **71**, 1635–1643 (2013).
6. Heath, E.I. *et al.* A phase I study of the pharmacokinetic and safety profiles of oral pazopanib with a high-fat or low-fat meal in patients with advanced solid tumors. *Clin. Pharmacol. Ther.* **88**, 818–823 (2010).
7. Cho, B.C. *et al.* ASCEND-8: a randomized phase 1 study of ceritinib, 450 mg or 600 mg, taken with a low-fat meal versus 750 mg in fasted state in patients with anaplastic lymphoma kinase (ALK)-rearranged metastatic non-small cell lung cancer (NSCLC). *J. Thorac. Oncol.* **12**, 1357–1367 (2017).
8. Abbas, R., Hug, B.A., Leister, C., Gaaloul, M.E., Chalon, S. & Sonnichsen, D. A phase I ascending single-dose study of the safety, tolerability, and pharmacokinetics of bosutinib (SKI-606) in healthy adult subjects. *Cancer Chemother. Pharmacol.* **69**, 221–227 (2012).
9. Parsad, S. & Ratain, M.J. Food effect studies for oncology drug products. *Clin. Pharmacol. Ther.* **101**, 606–612 (2017).
10. Szmulewitz, R.Z. *et al.* Prospective international randomized phase II study of low-dose abiraterone with food versus standard dose abiraterone in castration-resistant prostate cancer. *J. Clin. Oncol.* **36**, 1389–1395 (2018).
11. US Food and Drug Administration (FDA). Ceritinib (Zykadia) product label <https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/205755s010lbl.pdf>. Accessed November 1, 2018.
12. Suttle, A.B. *et al.* Relationships between pazopanib exposure and clinical safety and efficacy in patients with advanced renal cell carcinoma. *Br. J. Cancer* **111**, 1909–1916 (2014).
13. Verheijen, R.B., Swart, L.E., Beijnen, J.H., Schellens, J.H.M., Huitema, A.D.R. & Steeghs, N. Exposure-survival analyses of pazopanib in renal cell carcinoma and soft tissue sarcoma patients: opportunities for dose optimization. *Cancer Chemother. Pharmacol.* **80**, 1171–1178 (2017).
14. Hutson, T.E. *et al.* Efficacy and safety of pazopanib in patients with metastatic renal cell carcinoma. *J. Clin. Oncol.* **28**, 475–480 (2010).
15. Ruddy, K., Mayer, E. & Partridge, A. Patient adherence and persistence with oral anticancer treatment. *CA Cancer J. Clin.* **59**, 56–66 (2009).
16. Trask, P.C., Tellefsen, C., Espindle, D., Getter, C. & Hsu, M.A. Psychometric validation of the cancer therapy satisfaction questionnaire. *Value Health* **11**, 669–679 (2008).
17. Abetz, L. *et al.* Development of the cancer therapy satisfaction questionnaire: item generation and content validity testing. *Value Health* **8** (suppl. 1), S41–S53 (2005).
18. van Erp, N.P., de Wit, D., Guchelaar, H.J., Gelderblom, H., Hessing, T.J. & Hartigh, J. A validated assay for the simultaneous quantification of six tyrosine kinase inhibitors and two active metabolites in human serum using liquid chromatography coupled with tandem mass spectrometry. *J. Chromatogr. B Analyt. Technol. Biomed. Life Sci.* **937**, 33–43 (2013).
19. Diletti, E., Hauschke, D. & Steinijans, V.W. Sample size determination for bioequivalence assessment by means of confidence intervals. *Int. J. Clin. Pharmacol. Ther. Toxicol.* **29**, 1–8 (1991).
20. de Wit, D. *et al.* Therapeutic drug monitoring to individualize the dosing of pazopanib: a pharmacokinetic feasibility study. *Ther. Drug Monit.* **37**, 331–338 (2015).
21. Altman, D.G. *Practical Statistics for Medical Research*. 1st edn., 467 (Chapman & Hall, London, 1991).