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Results from in vitro and in vivo studies evaluating the bioavailability, effects of food, and administration as crushed tablet suspension on vericiguat pharmacokinetics

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Abstract

Objective: This article describes in vitro and in vivo studies that aimed to further characterize the biopharmaceutical properties and pharmacokinetic (PK) profile of vericiguat and to guide dosing recommendations.

Methods: Five open-label, phase I studies characterized the biopharmaceutical aspects of vericiguat, including absolute bioavailability, bioavailabilities of different formulations, dose proportionality, and food effect. Area under the curve (AUC) and maximum plasma concentrations (C_{max}), determined by a noncompartmental analysis, were compared by analysis of variance, and a mixed-effects power model was used to assess dose proportionality. The effect of food on the dissolution of vericiguat was evaluated in vitro using media simulating the gastrointestinal tract under fed and fasted conditions. In vitro dissolution of intact vs crushed vericiguat tablet was assessed in quality control medium (HCl at pH 2), acetate buffer at pH 4.5, and phosphate buffer at pH 6.8.

Results: Dissolution of vericiguat increased under fed conditions. In healthy subjects, exposure (AUC and C_{max}) increased ~ 40% with food vs fasted state (10 mg intact tablet) confirming a food effect on vericiguat bioavailability. Interindividual variability in exposure decreased ~ 20%, irrespective of meal type. Absolute bioavailability of vericiguat 10 mg (intact tablets, fed) was 93%. Vericiguat 2.5–10 mg demonstrated dose proportionality (intact tablets, fed) in healthy subjects. Dissolution studies showed no differences between the formulations, and this was confirmed with in vivo studies.

Conclusion: Vericiguat tablets should be administered with food and may be crushed for patients who have difficulty swallowing.

Keywords: Crushed, Dissolution, Heart failure, Dose proportionality, Bioavailability

This work was presented in part as a poster at the American Association of Pharmaceutical Scientists (AAPS) annual meeting 2019.

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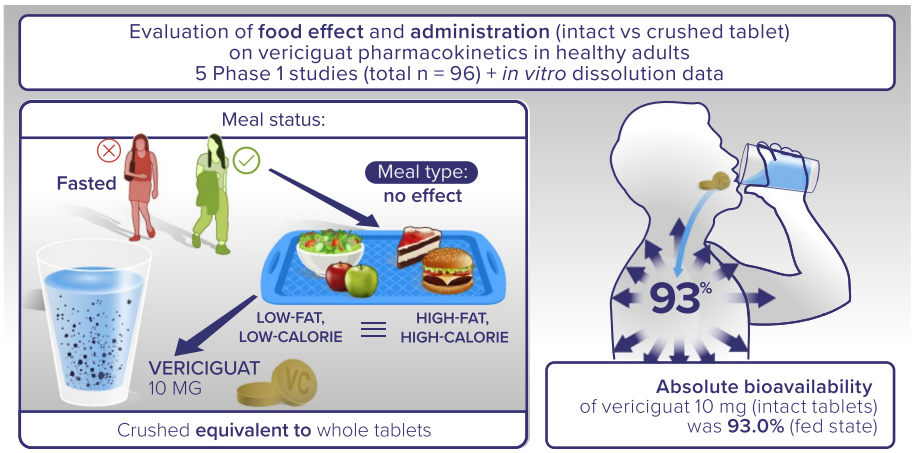
Graphical Abstract



Introduction

Vericiguat is a soluble guanylate cyclase stimulator, indicated to reduce the risk of cardiovascular death and heart failure (HF) hospitalization following a hospitalization for HF or need for outpatient intravenous (IV) diuretics, in adults with symptomatic chronic HF and ejection fraction less than 45% (Food and Drug Administration 2021a). The recommended starting dose of vericiguat is 2.5 mg orally once daily with food. The dose should be doubled approximately every 2 weeks to reach the target maintenance dose of 10 mg once daily, as tolerated by the patient (Food and Drug Administration 2021a).

Within the clinical development program, several formulations of vericiguat were investigated (Supplementary Table S1); however, vericiguat was primarily administered as immediate-release (IR) tablets with a non-functional film coating. Vericiguat has low solubility, high permeability, and is a weakly basic compound (Becker et al. 2019), in line with a Biopharmaceutics Classification System (BCS) class II drug (Food and Drug Administration 2017). Vericiguat IR tablets have predictable pharmacokinetics (PKs), with peak plasma concentration reached at approximately 4 h after oral administration with food in healthy adults and a mean elimination half-life of approximately 20–24 h (Boettcher et al. 2021a; European Medicines Agency 2021), consistent with a pharmacological profile suitable to once daily dosing. In phase I studies, vericiguat was generally well-tolerated and most treatment-emergent adverse events (TEAEs) were of mild intensity (Boettcher et al. 2021a). The most frequent TEAE in the discussed studies were "headache", "nasopharyngitis", "increased blood creatine phosphokinase", "nausea", and "dyspepsia", reported in 33.3%, 10.8%, 7.8%, 5.9%, and 5.9% of subjects, respectively. The hemodynamic effects of vericiguat were evaluated and found to be consistent with its mode of action (Boettcher et al. 2021a). Vericiguat also has a low potential for PK and pharmacodynamic interactions with other frequently prescribed medicines (Boettcher et al. 2020, 2021b). Glucuronidation to produce the pharmacologically inactive metabolite, M-1, is the main metabolic pathway of vericiguat; 53% is excreted in urine (primarily as M-1) and 45% in feces (primarily as vericiguat) (Boettcher et al. 2020).

Here, we describe the results of five phase I studies that aimed to further characterize the biopharmaceutical properties and PK profile of vericiguat. The studies evaluated the absolute oral bioavailability and general biopharmaceutical characteristics of different formulations and doses of vericiguat in the fed and fasted states, including the effect of different types of meals (high-fat, high-calorie or low-fat, low-calorie meal). As the presence of food alters the components of gastrointestinal fluid, in vitro dissolution studies with simulated intestinal fluids (representing fed and fasted states) were also performed. The findings of these studies informed the choice of dose administration (with food) in the phase IIb SOCRATES studies (NCT01951625 and NCT01951638) and the phase III VICTORIA trial (NCT02861534), and the recommendation in the prescribing information to take vericiguat with food (Food and Drug Administration 2021a).

Some patients with chronic HF that may require treatment with vericiguat, such as those who are geriatric, hospitalized, seriously ill, or have multiple comorbidities, may be fed by nasogastric tube or be unable to swallow the whole tablet formulation; therefore, crushing the

whole tablet formulation offers an alternative approach to whole tablets and is of clinical value (Food and Drug Administration 2018). Thus, an additional aim of the phase I studies was to evaluate the PK and bioavailability of vericiguat administered as a crushed tablet suspension relative to the intact tablet, to guide dosing recommendations for this patient group. To support this clinical study, in vitro studies were conducted to examine the influence of crushing the tablet on dissolution.

Overall, this article complements the PK characterization of vericiguat (Boettcher et al. 2021a, 2020, 2021b) and presents unpublished data on its biopharmaceutical properties.

Materials and methods

In vitro studies

Solubility and permeability

The solubility of vericiguat was determined by adding crystalline drug substance in excess to aqueous media (hydrochloric acid [HCl] pH 2, glycine buffer pH 3, acetate buffer pH 4.5, and phosphate buffer pH 6.8). Suspensions were stirred at 37 °C for 24 h. The suspensions were then passed through a 0.45-µm membrane filter, and the clear filtrate was analyzed by high-performance liquid chromatography (HPLC) for vericiguat content.

The permeability of vericiguat was determined as previously described for the apical (A) to basal (B) and B-to-A orientation at 2 µM using a validated Caco-2 cell assay (International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) 2019; Wunder et al. 2009).

Evaluation of dissolution

Fed vs fasted state To support in vivo PK observations in the fed and fasted states, the effect of food on dissolution was evaluated using media simulating the gastrointestinal tract under fed and fasted conditions. Intact vericiguat tablets at doses of 2.5 mg, 5 mg, and 10 mg were added to 500 mL of fasted-state simulated intestinal fluid (FaSSIF) and 500 mL of fed-state simulated intestinal fluid (FeSSIF). Both FaSSIF and FeSSIF were prepared according to the manufacturer´s instructions (www.biorelevant.com, accessed Feb 28, 2022). Dissolution studies were performed at 37 °C using United States Pharmacopeia 2 paddle apparatus with a stirring speed of 75 rpm. Ten milliliters of samples manually drawn from each of the dissolution vessels at time points 5, 10, 15, 20, 30, 40, 50, and 60 min were filtered using 0.45 µm regenerated cellulose filters (Whatman Spartan, Cytiva, Germany). For each sampling time point and vessel, a fresh filter was used. Pre-rinse volume for filtration was 6 mL. Withdrawn sampling volume was replaced by adding 10 mL of fresh FaSSIF or FeSSIF medium to each vessel after every sampling time point, respectively. Vericiguat content in the filtrate was determined by HPLC with UV-detection (Agilent, Waldbronn, Germany; Supplementary Table S2).

Crushed vs intact tablets To investigate the influence of crushing the tablet, dissolution of intact tablet and crushed tablet suspension (2.5 mg and 10 mg) were compared in the quality control medium (900 mL 0.01 M HCl; pH 2) as well as in 900 mL of acetate buffer pH 4.5 and 900 mL of phosphate buffer pH 6.8, respectively. Dissolution studies were performed at 37 °C using United States Pharmacopeia 2 paddle apparatus with a stirring speed of 75 rpm. Ten milliliters of samples manually drawn from each of the dissolution vessels at time points 15, 30, 45, and 60 min were filtered using either 0.45 µm regenerated cellulose filters (Whatman Spartan, Cytiva, Germany; for each sampling time point and vessel, a fresh filter was used; pre-rinse volume for filtration was 6 mL; withdrawn sampling volume was replaced by adding 10 mL of fresh dissolution medium to each vessel after every sampling time point, respectively), or validated filter equivalents (e.g., G4 glass frit as part of the fully automated dissolution system RoboDisI, Erweka, Germany). Filtrates were subjected to quantification by validated HPLC methods (Agilent, Waldbronn, Germany; Supplementary Table S2).

The preparation of the tablet suspensions for in vitro dissolution testing followed the suspension preparation conducted for the vericiguat coated tablet 10 mg in the respective human PK study (Supplementary Table S1).

As the tablet suspension may sit for a few hours after preparation until administration in the clinical setting, a short-term stability study over 4 h was conducted for the crushed tablet suspension, consistent with the regulatory guidance (Food and Drug Administration 2018). For crushed tablets, dissolution was evaluated for the suspension applied to the dissolution medium immediately and 4 h (at room temperature) after preparation. Statistical comparison of dissolution curves was performed using the F2 test according to guidelines (International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) 2019; Moore and Flanner 1996; Food and Drug Administration 2021).

Phase I clinical studies

Five separate, open-label, non-placebo-controlled, single-dose, and single-center clinical studies (Table 1) were conducted between December 2011 and August 2017. All

Table 1 Five phase I studies of vericiguat in healthy subjects

Study title and EudraCT#	Vericiguat dose, formulation, and fed/fasted state	Study objectives, description and numbers of subjects who completed the studies
Relative bioavailability 2011–004,841-42	1.25 mg intact tablet (fasted), 5 mg intact tablet (fed and fasted), 5 mg PEG solution (fasted)	Safety, PD, and PK of vericiguat intact tablets vs PEG solution Four-way, crossover design ($n=15$) Healthy, White males
Absolute bioavailability 2015–001,568-20	10 mg tablets (two 5 mg intact tablets; fed, high-fat, high-calorie meal), followed by 20 µg (^{14}C-labeled) IV infusion over 30 min (4 h post-oral tablet)	Absolute bioavailability of a single oral dose of vericiguat 10 mg (fed state) vs a single IV infusion microdose (20 µg) of ^{14}C-labeled vericiguat Non-randomized (all subjects received the same treatment; $n=10$) Healthy, White males
Exploratory dose proportionality 2012–004,839-23	1.25 mg, 2.5 mg, 5 mg, and 10 mg intact tablets (all fed, high-fat, high-calorie meal)	PK and safety of vericiguat 1.25–10 mg (fed state) Four-way crossover study ($n=15$) Healthy, White males
Pivotal food effect and dose proportionality 2016–000,980-18	2.5 mg, 5 mg, and 10 mg intact tablets (all fed) 10 mg tablets (fasted)	PK dose proportionality of single oral dose of vericiguat 2.5 mg and 5 mg vs 10 mg (fed) Food effect on PK after single oral dose of 10 mg (fed vs fasted) Safety of vericiguat Four-way crossover study ($n=29$ [food effect]; $n=27$ [dose proportionality]) Healthy, White males
Comparative bioavailability[a] 2016–005,074-35	10 mg crushed tablets suspension (fed, high-fat, high-calorie meal) 10 mg intact tablet (fed, high-fat, high-calorie or low-fat, low-calorie meal)	PK of crushed tablet suspension vs intact tablets in fed conditions (high-fat vs low-fat meal) Six-way crossover study ($n=27$) Healthy, White males

All studies were randomized and included a washout phase of ≥ 5 days between treatments, except for the absolute bioavailability study, which was non-randomized and had no washout. *N* numbers are the numbers of subjects that completed the studies. For the pivotal food effect study, 29 subjects completed the study (27 were included in the PK analysis set for dose-proportionality)

IV Intravenous, *PD* Pharmacodynamic, *PEG* Polyethylene glycol, *PK* Pharmacokinetic

[a] Three of six treatments from this study are presented

studies, except for the absolute bioavailability study, were crossover studies comparing multiple treatment regimens, with subjects randomized to treatment sequence. Healthy, white, male subjects aged ≥ 18 and ≤ 55 years with a body mass index (BMI) of ≥ 18.0 and ≤ 30.0 kg/m^2 who provided written informed consent were eligible for participation. Exclusion criteria included the use of regular medication within 4 weeks of study drug administration and the use of medications that may have interfered with the study drug at least 2 weeks prior to dosing. Studies met all local and regulatory requirements and were conducted in accordance with the currently accepted version of the Declaration of Helsinki and the International Conference on Harmonization Good Clinical Practice (GCP) Guideline.

The oral formulations used in the studies were intact IR tablets, crushed IR tablets suspended in water, and a polyethylene glycol (PEG) solution formulation (Supplementary Table S1). Vericiguat was also administered as an IV infusion in the absolute bioavailability study. These four vericiguat formulations are referred to here as: intact tablets, crushed tablet suspension, PEG solution, and IV infusion.

Relative bioavailability and food effect study

The bioavailability of vericiguat intact tablets (1.25 mg and 5 mg) relative to that of PEG solution (5 mg) was assessed in a four-way crossover study (Study 2011–004,841-42; Table 1). The PEG solution was the formulation utilized in the first-in-human (FIH) studies, because the FIH studies were performed before the tablet formulation was completed and because this oral solution allows all dosing increments to be administered while ensuring independence of dissolution. This study compared the PEG and tablet formulations to bridge the results from the FIH studies. The study also investigated the effect of food (high-fat, high-calorie meal) on the PK of the intact tablet (5 mg).

Evaluation of absolute bioavailability

The absolute bioavailability of a single oral dose of vericiguat 10 mg, administered as two 5 mg intact tablets in the fed state, was characterized using a micro-dose approach (Study 2015–001,568-20; Table 1). The study utilized simultaneous administration of oral vericiguat and a ^{14}C-labeled micro-dose of 20 µg vericiguat as

a comparator. The micro-dose was administered as a 30-min IV infusion, 4 h after oral tablet dosing, coinciding with the approximate time (T_{max}) to reach maximum plasma concentration (C_{max}) of the intact tablet formulation.

Dose proportionality

Dose proportionality of vericiguat administered as intact tablets was examined in two studies (Study 2012–004,839-23 and Study 2016–000,980-18; Table 1), across the dose range 1.25 mg to 10 mg.

Evaluation of food effects and meal type

The effect of food on vericiguat PK was characterized in the pivotal food effect and dose proportionality study (Study 2016–000,980-18; Table 1). Vericiguat was administered either without food (fasted state) or with a high-fat, high-calorie or a low-fat, low-calorie meal (fed state). Meals were ingested 30 min before treatment. When vericiguat was taken in the fasted state, subjects underwent an overnight fast for at least 10 h before receiving the study drug. Drinking of water was permitted until 2 h pre-dose. Food and beverages on the day of dosing were standardized. Neither were allowed during the first 2 h post-dose. Water consumption only (up to 250 mL) was allowed 2–4 h post-dose. Subjects received a standardized lunch, snack, and dinner (approximately 4, 8, and 12 h post-dose, respectively).

In line with international regulatory guidelines and recommendations for food effect studies, the high-fat, high-calorie meal contained 50% fat, with calorific content at approximately 800–1000 kcal (Food and Drug Administration 2002). Conversely, in line with draft guidance, the low-fat, low-calorie meal contained 25% fat, with calorific content at 407 kcal (Food and Drug Administration 2019). A content breakdown of test meals by carbohydrate, fat, and protein content is given in Table 2.

Table 2 Breakdown of high-fat, high-calorie and low-fat, low-calorie meals

	High-fat, high-calorie meal	Low-fat, low-calorie meal
Fat content, g (kcal)	63.5 (584.2)	24.8 (222)
Protein content, g (kcal)	42 (176.4)	6 (25)
Carbohydrate content, g (kcal)	67 (281.4)	36.5 (160)
Total calories (kcal)	1042	407

Example of high-fat, high-calorie meal: two large eggs fried in 10 g butter, two slices of fried ham, two slices of toast, 20 g butter, pan-fried potatoes, milk with 3.5% fat and 100–150 mL decaffeinated coffee

Example of a low-fat/low-calorie meal: two slices of toasted white bread with butter and jam, cheese (45% fat) and 200 mL of tea with a cube of sugar (approximately 3 g)

Relative bioavailability of crushed tablets

The bioavailability of a crushed tablet suspension of vericiguat (10 mg) was examined relative to intact tablets (10 mg) under fed conditions (Study 2016–005,074-35; Table 1).

Study assessments and analyses

Blood samples for PK analyses were collected pre-dose and at 30-min intervals for the first 5 h, and at regular intervals (1–24 h) up to 72 h after single-dose administration. Vericiguat plasma concentrations were determined after protein precipitation followed by liquid chromatography mass spectrometry with tandem mass spectrometric detection, with quantitation being achieved by weighted linear regression using stable isotope-labeled internal standards (Boettcher et al. 2021a). The determined analyte concentrations in study samples were verified by assaying quality control samples of blank matrix spiked with known concentrations of the respective analytes. Concentrations above the lower limit of quantification (LLOQ) were determined with a precision within 15% and an accuracy within 85–115%, and concentrations at the LLOQ were determined with a precision of 20% and an accuracy within 80–120%.

PK parameters were calculated with WinNonlin (versions 4.1a and 5.3, Pharsight Corporation, Mountain View, CA, USA) and included area under the curve (AUC), C_{max}, and dose-normalized AUC and C_{max} (AUC/D and C_{max}/D, respectively).

For evaluation of absolute bioavailability, AUC/D and C_{max}/D of vericiguat and ^{14}C-labeled vericiguat, determined by noncompartmental analysis, were analyzed by analysis of variance (ANOVA) including treatment and subject effects. Point estimates (least squares means) and exploratory 90% confidence intervals (CIs) were calculated for ratios between treatments. The absolute bioavailability (F) of vericiguat was defined as the AUC/D ratio of 10 mg intact vericiguat tablets to ^{14}C-labeled 20 µg vericiguat IV infusion.

To compare the different formulations and treatments, the parameters AUC/D and C_{max}/D of vericiguat were analyzed using ANOVA including sequence, subject (sequence), period, and treatment effects. Bioequivalence was determined if 90% CIs for PK ratios for AUC and C_{max} were within the limits of 0.80–1.25.

For the evaluation of dose proportionality of vericiguat, three different doses (2.5 mg, 5 mg, and 10 mg, with food) were evaluated with respect to their bioavailability. A mixed-effects power model (i.e., a linear regression between log-transformed AUC and C_{max} and the logarithm of the dose) was used to assess dose proportionality (Sethuraman et al. 2007; Smith et al. 2000). The

90% CI acceptance range for dose proportionality was 84–116%.

Vericiguat PK results are presented from each study. Subjects with valid PK profiles for at least two treatments were included in the PK analyses. Study periods were considered invalid for PK analysis if pre-dose concentrations were larger than 5% of C_{max} (Food and Drug Administration 2014), an invalid PK reading indicated that the subject had not ingested the tablet, or were deemed invalid due to a protocol deviation.

Safety assessment

Safety results from the five studies were pooled. As part of the safety evaluation, blood pressure, heart rate, and electrocardiograms (ECGs) were recorded. The safety analysis set comprised all subjects who received the study drug.

Results

In vitro studies

Solubility

Vericiguat is a lipophilic (logP 2.99), weakly basic (pKa 4.19) compound. In line with its pKa value, solubility is pH-dependent. Solubility values were 0.9, 2, 26, and 247 mg/L in phosphate buffer pH 6.8, acetate buffer pH 4.5, glycine buffer pH 3, and HCl pH 2, respectively, resulting in dose/solubility ratios of 11,111 mL (pH 6.8), 5000 ml (pH 4.5), 385 mL (pH 3), and 40 mL (pH 2), respectively. Therefore, vericiguat is a low solubility compound according to the definition of the BCS.

Permeability

Vericiguat showed a high permeability with P_{app} values of 111 ± 22 nm/s for the A-to-B direction and 464 ± 37 nm/s for the B-to-A direction across Caco-2 cells. Based on these data, an efflux ratio of 4.21 was calculated suggesting an active efflux.

Dissolution

Fed vs fasted Dissolution of the intact vericiguat 10 mg tablet was increased in FeSSIF compared with FaSSIF (both 500 mL; Fig. 1). Similar results were observed for vericiguat 2.5 mg and 5 mg tablets (not shown).

Crushed vs intact tablet Figure 2A, B and C shows the dissolution curves for vericiguat 10 mg of intact tablet and crushed tablet suspension applied to dissolution medium immediately after preparation, and crushed tablet suspension applied to dissolution medium 4 h after preparation. Individual data for each tablet are shown in Supplementary Tables S3, S4 and S5. With HCl pH 2 as dissolution medium, dissolution was complete in all cases. No relevant difference was detected between crushed and intact tablet formulations in the quality control medium. Comparison of the curves for crushed tablet suspension immediately and 4 h after preparation were similar, indicating that vericiguat was stable in crushed tablet suspension for 4 h at room temperature, and that no aggregation of suspended particles occurred during the storage time. As complete dissolution was observed (100% amount dissolved), no sample loss occurred during the procedure of crushing the tablet and transferring the crushed tablet into the vessel and thus, the subject in the respective clinical trial. Another concern of crushing the tablet is that crushing may potentially lead to faster dissolution due to higher surface area, and in consequence to faster absorption, which could translate into higher C_{max} values. An even faster dissolution of crushed tablet

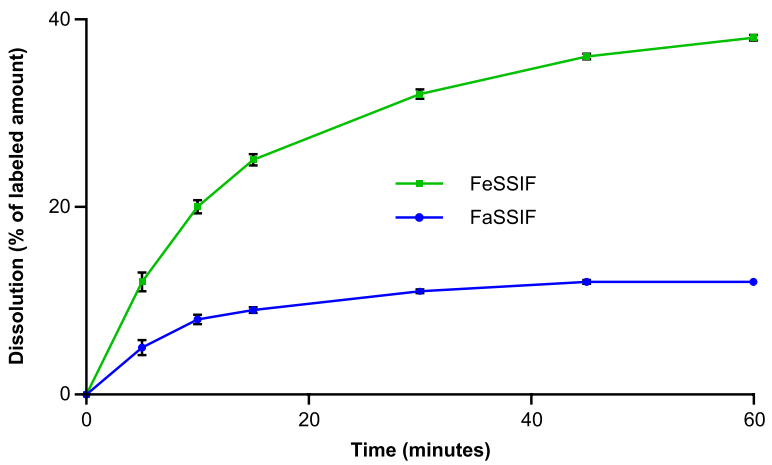


Fig. 1 Mean dissolution of vericiguat 10 mg intact tablet in FaSSIF and FeSSIF (both 500 mL; $n = 6$). 95% confidence interval bars are contained within the data symbols. *FaSSIF*, fasted state-simulated intestinal fluid; *FeSSIF*, fed state-simulated intestinal fluid

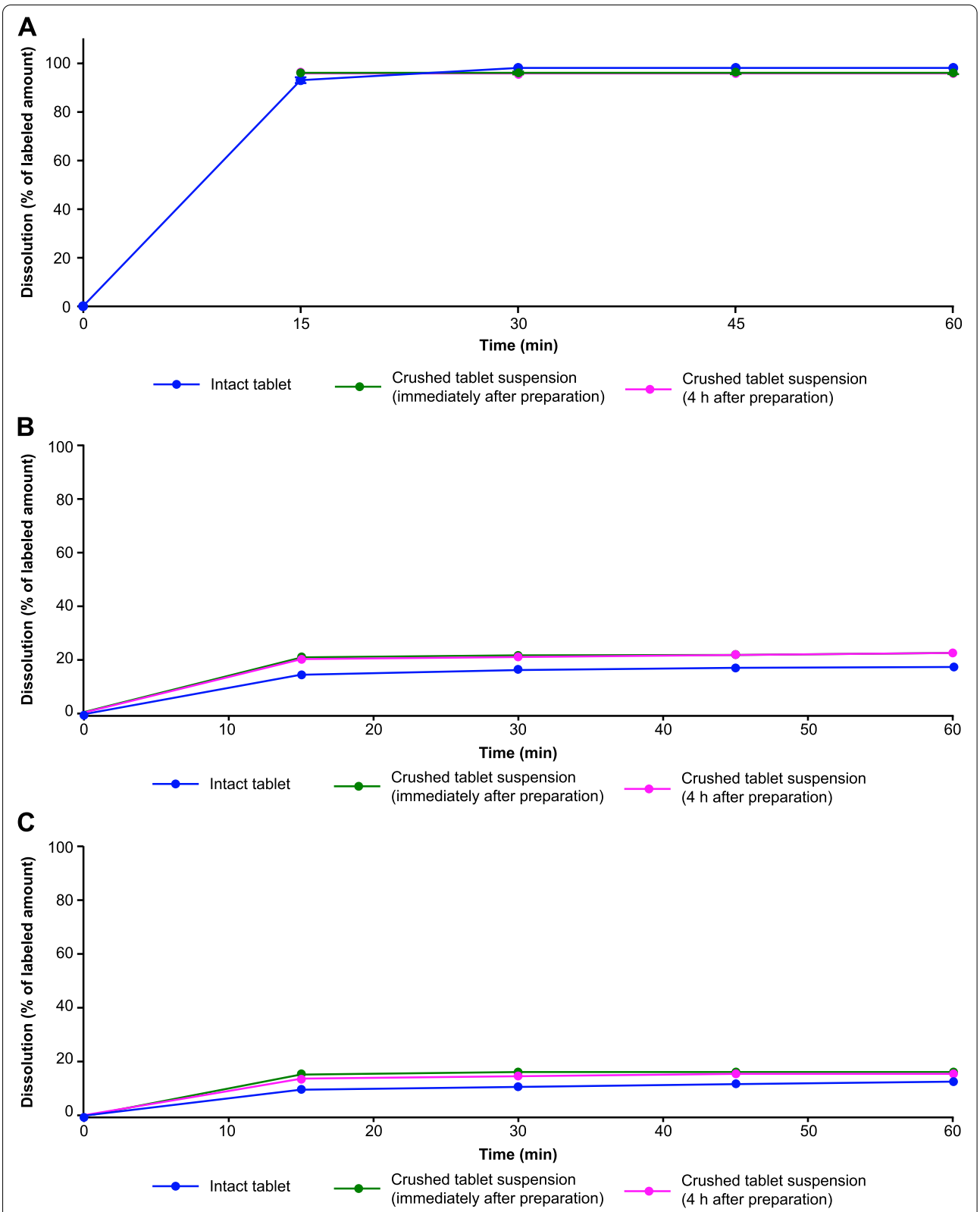


Fig. 2 Dissolution of vericiguat 10 mg as an intact tablet, crushed tablet suspension immediately after preparation, and as a crushed tablet suspension 4 h after preparation ($n = 12$) in 900 mL of **A** 0.01 M HCl pH2, **B** acetate buffer pH 4.5, and **C** phosphate buffer pH 6.8, at 37°C at 75 rpm. 95% confidence interval bars are contained within the data symbols

versus intact tablet cannot be demonstrated in the acidic quality control medium because dissolution after 15 min was already complete for both crushed and intact tablets. Therefore, dissolution at higher pH was performed, using the media acetate buffer pH 4.5 and phosphate buffer pH 6.8, as recommended by various guidances on comparative in vitro dissolution testing, e.g., ICH M9 (International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) 2019). pKa- and pH-dependent solubility of vericiguat demonstrated a strong decrease in solubility between pH 2 and 3 (and further from 3 to 4.5 and 6.8), in line with the pKa value of ~ 4. In line with this, lower dissolution of vericiguat from tablets was observed in dissolution media acetate buffer pH 4.5 (Fig. 2B) and phosphate buffer pH 6.8 (Fig. 2C). However, no difference in dissolution between the intact tablet and crushed tablet suspension was observed at a higher pH, as indicated by pairwise F2 calculations (Table 3). In all cases, the F2 value was > 50. Furthermore, the in-use stability study of the crushed tablet suspension over 4 h at room temperature revealed no difference in dissolution at pH 4.5 and pH 6.8 (Table 3; Fig. 2B, C), as F2 values were > 50 in all cases.

Data are shown for the 10 mg tablet. Similar findings were observed for the 2.5 mg dose (not shown).

Phase I clinical studies

Subjects

Across the five studies described here (Table 1), a total of 96 White males enrolled and completed treatment. The mean age of all subjects and mean BMI ranged from 28.1 to 38.5 years and 23.7 to 25.0 kg/m^2, respectively, across studies. Five subjects withdrew from their respective studies early. Of these five subjects, two discontinued due to TEAEs (described below), one subject was withdrawn at the investigator's decision due to the omission of a treatment period, another subject reported behavioral changes (that were considered not drug-related), and one was withdrawn due to a positive alcohol test.

Table 3 Statistical comparison between intact and crushed 10 mg vericiguat tablet (in 900 mL acetate buffer at 37°C at 75 rpm) expressed as F2 value for each pair

pH of dissolution medium	F2 value	
	Intact tablet vs crushed tablet (immediately after dispersion)	Intact tablet vs crushed tablet (4 h after dispersion)
4.5	64	64
6.8	64	70

Pharmacokinetics

Absolute and relative bioavailability Under fed conditions, oral bioavailability of vericiguat was near complete, as vericiguat 10 mg (administered orally as two intact 5 mg tablets) followed by IV infusion of [^{14}C] vericiguat 20 µg had an AUC/D relative to IV infusion of 93% (Table 4; Supplementary Figure S1 and S2).

In the fasted state, the relative bioavailability of 5 mg vericiguat was reduced following administration as intact tablets relative to the PEG solution (Supplementary Figure S3 and S4). The AUC of the tablet was 29% lower and the C_{max} was 40% lower than the PEG solution. Oral administration of vericiguat 1.25 mg intact tablet showed similar bioavailability to the 5 mg PEG solution, based on dose-normalized exposure.

Effect of food The effect of food on the PK of vericiguat indicated by the dissolution studies was confirmed in vivo. For both 5 mg and 10 mg vericiguat doses, administration of the intact vericiguat tablet with food increased median T_{max} from 1.5–2.0 h (fasted) to 4.0–4.5 h (fed). At the 5 mg dose, vericiguat AUC and C_{max} increased by 19% and 9%, respectively, with food relative to the fasted state and the 90% CIs were slightly above the upper limit for bioequivalence. The interindividual variability of PK parameters reduced when vericiguat 5 mg was administered with food: the coefficient of variation (CV) was 20–45% in the fasted state and < 20% with food.

At the 10 mg dose, AUC and C_{max} were further increased by 44% and 41%, respectively, when administered with food (high-fat, high-calorie meal) compared with the fasted state, with 90% CIs above the limit of bioequivalence (Table 5; Supplementary Figure S5, S6, S7 and S8). AUC was 5600 µg*h/L and 3890 µg*h/L in the fed and fasted states, respectively. PK variability was reduced when vericiguat tablet was administered with food: the variability in exposure (AUC) was reduced to 19% from 41% and variability of C_{max} was reduced to 16% from 60% relative to the fasted state.

Effect of type of food The type of meal consumed had no effect on AUC/D, with the 90% CIs for AUC/D falling within the limits for bioequivalence. However, 90% CI for C_{max}/D was above the upper limit. As this was only slightly over the upper limit and in line with the lower calorie count, and its lower effect on a delay of gastric emptying than a high calorie count, the increase in C_{max}/D with a low-fat, low-calorie meal relative to a high-fat, high-calorie meal was not considered clinically relevant (Table 5; Supplementary Figure S9 and S10).

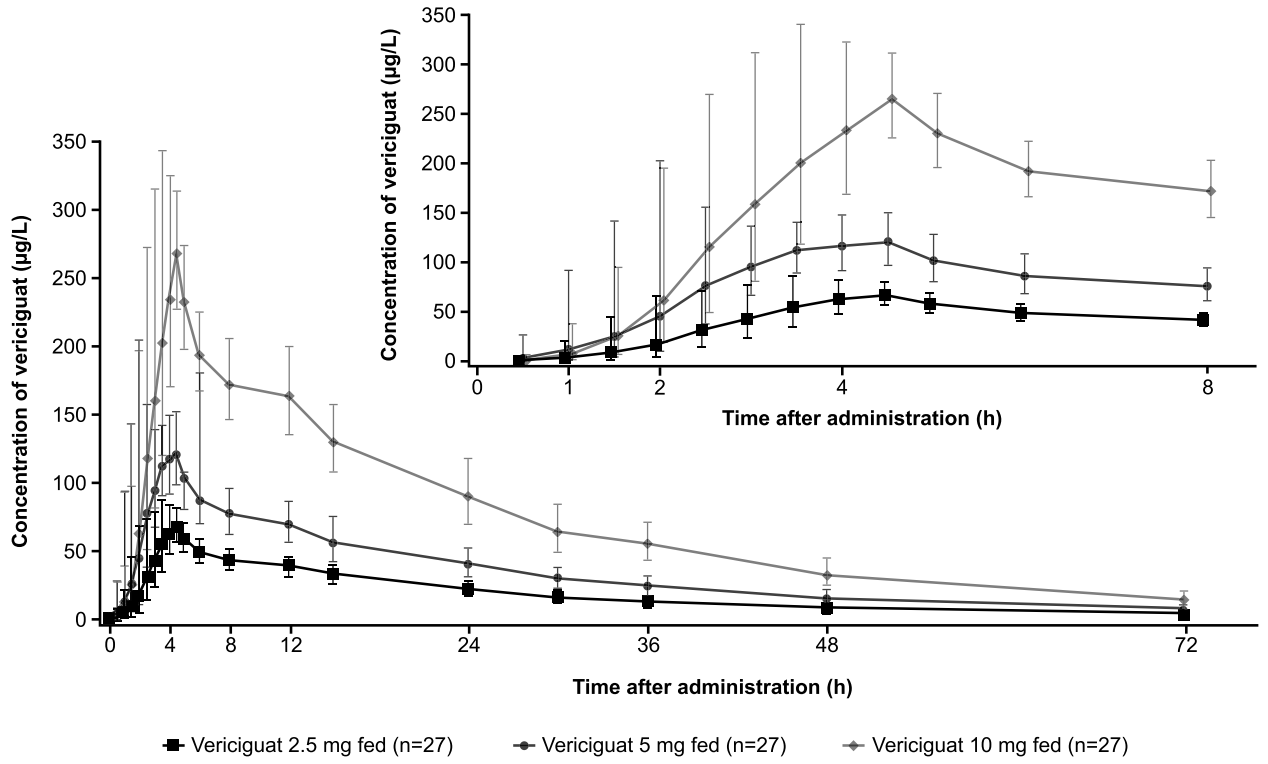


Fig. 3 Plasma concentrations of vericiguat (mg/L) after a single oral dose of vericiguat (intact tablet formulation, $n = 27$). Data from EudraCT# 2016–000,980-18

Table 4 Vericiguat bioavailability: point estimates (LS means) and two-sided 90% CIs of PK parameters after administration of vericiguat as intact tablets, PEG solution, and IV formulations

Comparison (test vs reference)	Parameter (unit)	*n*	CV (%)	Ratio (%)	90% CI
Relative bioavailability					
5 mg intact tablet (fasted)/5 mg PEG solution (fasted)	AUC, µg*h/L	15	15.69	70.56	64.09–77.68
	C_{max}, µg/L	15	27.68	59.94	50.69–70.88
1.25 mg intact tablet (fasted)/5 mg PEG solution (fasted)	AUC/D, h/L	15	15.69	92.38	83.91–101.70
	C_{max}/D, /L	15	27.68	92.85	78.53–109.79
Absolute bioavailability study					
10 mg intact tablets (fed)/20 µg IV infusion (fed)	AUC/D, h/L	10	4.23	93.03	89.86–96.31
	C_{max}/D, /L	10	10.17	42.61	39.21–46.31

ANOVA Analysis of variance, *AUC* Area under curve, *AUC/D* Dose-normalized area under the curve, *CI* Confidence interval, C_{max} Maximum plasma concentration, C_{max}/D Dose-normalized maximum plasma concentration, *CV* Coefficient of variation, *IV* Intravenous, *LS* Least squares, *PEG* Polyethylene glycol

Ratio: LS means for the respective treatment ratio calculated by ANOVA

Dose proportionality Overall, geometric mean AUC and C_{max} increased with increasing vericiguat doses (Fig. 3). In the exploratory dose-proportionality study, exposure of vericiguat 1.25–10 mg administered in the fed state increased in a dose-proportional manner. Further investigation on the pivotal food effect and dose proportionality study confirmed vericiguat PK was dose-proportional when taken with food. The point estimates for the slope of the linear regression between log-transformed AUC and C_{max}, respectively, and the logarithm of the dose (β) and the associated 90% CIs (Sethuraman et al. 2007; Smith et al. 2000) were within the acceptance range of 84–116% for dose proportionality (AUC: 100.8% [90% CI 94.1–107.5%]; C_{max}: 97.8% [90% CI 91.8–103.8%].

Table 5 Assessments of food and food type: point estimates (LS means) and two-sided 90% CIs of PK parameters after administration of vericiguat

Comparison (test vs reference)	Parameter (unit)	*n*	CV (%)	Ratio (%)	90% CI
Effects of food					
5 mg intact tablet (with food)/5 mg intact tablet (fasted)	AUC, µg*h/L	15	15.69	118.76	107.87–130.74
	$C_{max,}$ µg/L	15	27.68	109.23	92.38–129.15
10 mg intact tablet (with food)/10 mg intact tablet (fasted)	AUC, µg*h/L	29	28.02	143.79	127.08–162.69
	$C_{max,}$ µg/L	29	38.91	140.67	118.83–166.52
Effects of food type: low-fat, low-calorie or high-fat, high-calorie meal					
10 mg intact tablet (low-fat, low-calorie meal)/10 mg intact tablet (high-fat, high-calorie meal)	AUC/D, h/L	29	15.06	108.26	101.43–115.56
	C_{max}/D, /L	29	22.96	118.86	107.69–131.18

Geometric CV indicating intra-individual variability

ANOVA Analysis of variance, *AUC* Area under curve, *AUC/D* Dose-normalized area under the curve, *CI* Confidence interval, C_{max} Maximum plasma concentration, C_{max}/D Dose-normalized maximum plasma concentration, *CV* Coefficient of variation, *IR* Immediate release, *LS* Least squares, *PK* Pharmacokinetic

Ratio: LS means for the respective treatment ratio calculated by ANOVA

Effects of administering vericiguat as a crushed tablet suspension relative to intact tablets Findings from dissolution studies, which showed no differences between the formulations, were confirmed with in vivo studies. Plasma concentrations of vericiguat after administration of 10 mg crushed tablet suspension and 10 mg intact tablet with food are shown in Supplementary Figure S9 and S10. The relative bioavailability of vericiguat 10 mg as a crushed tablet suspension with respect to AUC and C_{max} was equivalent to intact tablets (with food), as demonstrated by ANOVA. The point estimates for the ratios of AUC/D and C_{max}/D were near unity (Fig. 4A, B) and exploratory 90% CIs were within the limits for bioequivalence (Table 6).

Safety

A pooled analysis of all four formulations of vericiguat up to 10 mg in 102 healthy subjects demonstrated that vericiguat was generally well-tolerated. No deaths or serious adverse events occurred. Of the two subjects who discontinued due to TEAEs, one was due to a TEAE of common cold, considered unrelated to the study drug, and the other subject was due to events of rash and pruritus, which were mild in intensity and judged by the investigator as related to vericiguat. No trends in the incidence of drug-related adverse events (AEs) were observed across any of the vericiguat formulations tested (14.8–24.7% for vericiguat up to 10 mg).

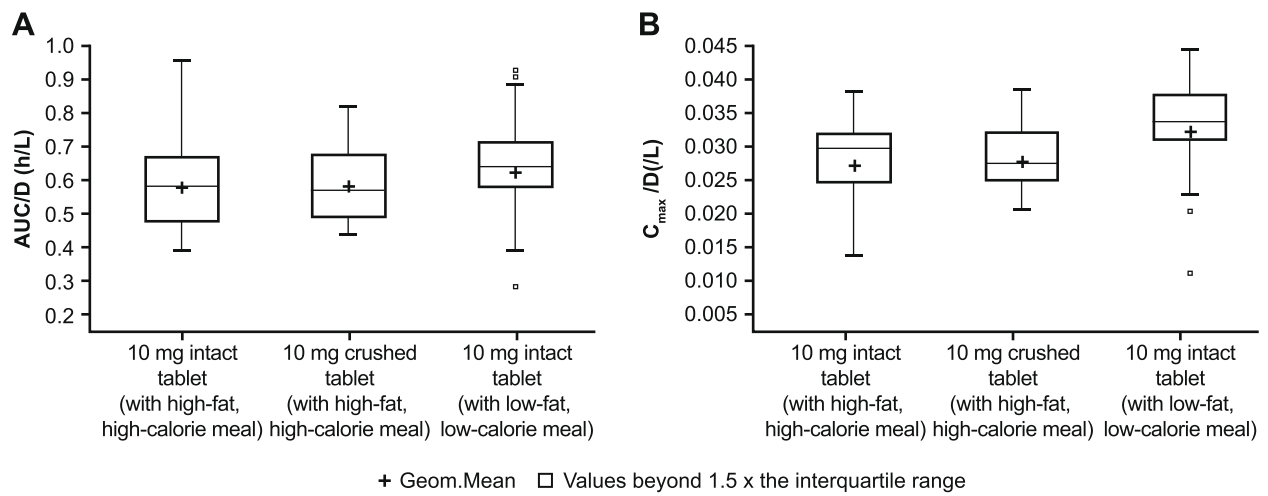


Fig. 4 Effects of crushing tablets: box plots for **A** AUC/D (h/L) and **B** C_{max}/D (/L) of vericiguat in plasma following a single oral dose administration of vericiguat 10 mg as intact tablets or as a crushed tablet suspension. Box plots represent the 25th to 75th percentiles; bold horizontal lines represent the median values. $n = 29$ for each treatment. *AUC/D*, dose-normalized area under the curve; *Cmax/D*, dose-normalized maximum plasma concentration

Table 6 Effects of crushing tablets on PK parameters of vericiguat: single oral dose administration of 10 mg intact or crushed tablet

Comparison (test vs reference)	Parameter (unit)	*n*	CV (%)	Ratio (%)	90% CI
Comparative bioavailability study					
10 mg crushed tablet (high-fat, high-calorie meal)/10 mg intact tablet (high-fat, high-calorie meal)	AUC/D, h/L	29	15.06	101.10	94.72–107.91
	C_{max}/D, /L	29	22.96	102.25	92.65–112.86

Geometric CV indicating intra-individual variability

AUC/D Dose-normalized area under the curve, *CI* Confidence interval, C_{max} Maximum plasma concentration, C_{max}/D Dose-normalized maximum plasma concentration, *CV* Coefficient of variation, *LS* Least squares, *PK* Pharmacokinetic

Ratio: LS means for the respective treatment ratio calculated by ANOVA

In total, 74 (72.5%) subjects experienced at least one TEAE. No TEAEs of severe intensity were reported.

The effects of vericiguat on vital signs, ECG, and laboratory test findings were consistent with the mode of action of vericiguat, and in line with the formulations tested.

Discussion

Vericiguat showed a typical biopharmaceutical profile for a BCS class II drug. The biopharmaceutical properties of different doses and formulations of vericiguat were characterized and included an evaluation of the bioavailability, impact of crushing the tablet, dose proportionality, and the effects of food on the PK profile of vericiguat, as well as an assessment of the effects of ingesting different meal types before receiving vericiguat.

We demonstrated that the absolute bioavailability of vericiguat administered as intact tablets relative to the IV formulation was high at 93% under fed conditions. Furthermore, the relative bioavailability assessments demonstrated that vericiguat administered as intact tablets resulted in delayed vericiguat absorption relative to the PEG solution formulation.

In biorelevant media, dissolution of the intact vericiguat tablet was increased in FeSSIF compared with FaSSIF, indicating a higher rate of vericiguat solution formation in the fed state relative to the fasted state (Fig. 1). In line with dissolution data, the effect of food on the PK of vericiguat was confirmed in vivo. Ingestion of the tablet with food reduced PK variability and increased vericiguat exposure compared with the fasted state.

With poorly soluble weak bases, the question of whether an increase in gastric pH after food intake (Koziolek et al. 2015a, 2015b) may decrease dissolution in the stomach resulting in a potential negative food effect must be considered. Alternatively, bile salts, lecithin, and food components may promote formulation and active pharmaceutical ingredient (API) wettening and dissolution, resulting in a positive food effect. As suggested by in vitro dissolution experiments in FaSSIF and FeSSIF (Fig. 1), the increased bioavailability of vericiguat after administration with food was likely due to improved solubility and dissolution due to bile salts and food components enhancing wettability and, therefore, improved absorption (Boettcher et al. 2021a). In a separate study (data not shown), dissolution of vericiguat tablets was recorded in a two-stage biorelevant dissolution model (slightly adapted from Mann et al. (Mann et al. 2017)) that represents gastric to intestinal transfer. Data revealed that under simulated fed conditions (stomach: 250 mL of fasted-state simulated gastric fluid (FaSSGF) adjusted to pH 4.0, dissolution recorded for 30 min; after 30 min 250 mL of a double concentrated FeSSIF was added to reach FeSSIF of pH 5.0, dissolution recorded for another 150 min), up to approximately 10% amount of API dissolved was observed in FaSSGF adjusted to pH 4.0. After addition of 250 mL of the double-concentrated FeSSIF, the dissolution curves in the resulting 500 mL of FeSSIF pH 5.0 were very similar to dissolution curves obtained in FeSSIF without the prior exposure of the tablets to FaSSGF pH 4.0. The presence of food also leads to a physiological effect whereby gastric emptying is delayed. This effect increased with an increasing amount of calorie intake. In line with this, a prolonged median $T_{\max}$ of the intact tablet demonstrated a delayed absorption in the fed state relative to the fasted state.

A limitation of dissolution studies in one-compartment dissolution systems is that they do not investigate complex mechanistic processes such as gastric emptying, potential vericiguat precipitation, and re-dissolution in the small intestine of vericiguat already dissolved in the stomach. Further investigation would be required to determine these processes. For example, data obtained from in vitro set-ups, in turn, can be used to inform a respective physiologically-based PK (PBPK) model (Kambayashi et al. 2016; Ruff et al. 2017; Pathak et al. 2017; Kourentas et al. 2016; Hens et al. 2017). A verified PBPK model of vericiguat and its major metabolite, M-1, has been developed based on in vitro and clinical PK data to provide a quantitative understanding of the disposition pathways and PK in healthy adults

(Frechen et al. 2020). Vericiguat could be tested in a human in vivo aspiration study, in which real-time dissolution and precipitation are measured in the stomach and small intestine by tube sampling after oral administration of respective formulations. Such studies have been performed for other poorly soluble weak bases such as dipyridamole, ketoconazole (Psachoulias et al. 2011) and posaconazole (Hens et al. 2016a, 2016b), and have been used as a backbone to calibrate in vitro multicompartment dissolution/precipitation set-ups. However, these types of investigations are beyond the scope of this article, but certainly of interest for the future.

As the calories of a meal can cause physiological gastrointestinal changes that affect systemic availability of a drug, we investigated two meal types (high-fat, high-calorie or low-fat, low-calorie), in accordance with guidelines (Food and Drug Administration 2019). The type of meal did not seem to have a clinically meaningful effect on the PK profile of vericiguat. Over the dose range studied, vericiguat had linear PK, demonstrating dose proportionality, consistent with previous studies (Boettcher et al. 2019). For BCS class II compounds, food effect is driven by bile salt solubilization, a response to the fat content often anticipated due to an increase in bile micelle concentrations. The lack of a meal-type effect for vericiguat supports the reasoning that for some BCS class II compounds the in vivo solubilization effect can be maximized with lower-fat-content meals compared with the standard meal commonly used in food effect studies or points to additional mechanisms, such as improved wetting facilitating dissolution, which may not require a large bile salt concentration.

In vitro dissolution studies also allowed a direct comparison between crushed versus intact tablets and complemented the respective clinical evaluations of the formulations. The dissolution study demonstrated that no vericiguat was lost during crushing and harvesting the crushed tablet, and that dissolution of the crushed tablet was not impaired by aggregation of the crushed tablet particles during the in-use stability study at room temperature. Furthermore, crushing the tablet did not increase the dissolution when compared with intact tablet, as indicated by comparative dissolution data in acetate buffer pH 4.5 and phosphate buffer pH 6.8. These in vitro dissolution data in media listed in the various bioequivalence guidelines (e.g., ICH M9 (International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) 2019)) reinforce the relevance of these in vitro dissolution media and conditions for the in vivo biopharmaceutical performance when it comes to formulation comparison.

Consistent findings were observed in in vivo studies, which demonstrated that systemic exposure or absorption (AUC and C_{max}) of vericiguat was comparable following administration of crushed tablet suspension and intact tablets in healthy subjects. One may speculate that there may be a difference in the rate of gastric emptying of vericiguat between intact and crushed tablets due to the magenstraße (stomach road) (Pal et al. 2007; Kiyota et al. 2022; Grimm et al. 2017), a normal physiological mechanism by which co-ordinated contraction waves move liquid content along a narrow path through the stomach to the duodenum (Pal et al. 2007). Faster gastric emptying of dissolved and finely dispersed drug may lead to earlier onset of peak plasma concentrations with the crushed tablet suspension. However, given that there were no relevant effects of crushing the tablet on C_{max}, it is unlikely that gastric emptying of vericiguat differed significantly between the intact tablet and crushed tablet suspension. Therefore, concerns that the administration of vericiguat as a crushed tablet suspension may alter systemic absorption were addressed here. These findings support the use of vericiguat in crushed tablet suspension as a viable method of administration and provide clinicians with an additional treatment option to administer vericiguat to very ill patients, or those with dysphagia, who are unable to swallow whole tablets.

Vericiguat was generally well-tolerated across the five phase I studies. The types of AE reported were consistent with the mode of action of vericiguat and no trends in the incidence of drug-related AEs were observed between vericiguat formulations. These data demonstrate that administration of vericiguat as an intact tablet or as a crushed tablet suspension was generally well-tolerated, with an acceptable safety profile.

The interpretation of the study results is potentially limited by missing data. Subjects were excluded from the analysis, in accordance with a standardized GCP-conformed process, if they had a study period that was invalid for PK analysis. Individual PK samples were excluded if they were damaged in transport. Missing data were not replaced; however, missing data were predicted and accounted for in the determination of sample size to ensure adequate statistical power for the analyses in those studies that were powered.

Conclusions

Oral bioavailability of vericiguat was near complete following administration of the intact tablet under fed conditions, and vericiguat PKs were dose-proportional when taken with food. Ingestion of the intact vericiguat tablet with food increased vericiguat exposure and reduced PK variability compared with the fasted state. Meal type had no clinically relevant effect on vericiguat exposure.

No relevant difference was detected between crushed and intact tablet formulations in in vitro dissolution

studies, and phase I studies demonstrated that, in the fed state, the relative bioavailability of vericiguat crushed tablets was equivalent to intact tablets. Vericiguat was stable in crushed tablet suspension for 4 h at room temperature.

Vericiguat was generally well-tolerated, with an AE profile consistent with its mode of action.

Overall, the findings from the in vitro and phase I studies presented here provided the basis for the dosing recommendation to administer vericiguat with food in the SOCRATES-REDUCED (Gheorghiade et al. 2015) and VICTORIA (Armstrong et al. 2020) studies, irrespective of meal type. These results also provide important guidance on the potential for administering vericiguat in crushed tablet formulation.

Abbreviations

AEs: Adverse events; API: Active pharmaceutical ingredient; AUC: Area under the curve; AUC/D: Dose-normalized AUC; ANOVA: Analysis of variance; BCS: Biopharmaceutics Classification System; BMI: Body mass index; CI: Confidence interval; C_{max}: Maximum plasma concentration; C_{max}/D: Dose-normalized C_{max}; CV: Coefficient of variation; ECGs: Electrocardiograms; F: Absolute bioavailability; FaSSIF: Fasted-state simulated intestinal fluid; FaSSGF: Fasted-state simulated gastric fluid; FeSSIF: Fed-state simulated intestinal fluid; HCl: Hydrochloric acid; HF: Heart failure; IR: Immediate-release; IV: Intravenous; PEG: Polyethylene glycol; PK: Pharmacokinetic; TEAEs: Treatment-emergent adverse events; T_{max}: Time to reach C_{max}.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s41120-022-00063-4.

Additional file 1: Table S1. Vericiguat formulations administered within the clinical development program. **Table S2**. HPLC conditions for determination of vericiguat content in filtrate in dissolution studies. **Table S3.** Dissolution of vericiguat 10 mg as an intact tablet, crushed tablet suspension immediately after preparation, and as a crushed tablet suspension 4 h after preparation in 900 mL 0.01M HCl pH 2 at 37°C at 75 rpm. **Table S4.** Dissolution of vericiguat 10 mg as an intact tablet, crushed tablet suspension immediately after preparation, and as a crushed tablet suspension 4 h after preparation in 900 mL acetate buffer pH 4.5 at 37°C at 75 rpm. **Table S5.** Dissolution of vericiguat 10 mg as an intact tablet, crushed tablet suspension immediately after preparation, and as a crushed tablet suspension 4 h after preparation in 900 mL acetate buffer pH 6.8 at 37°C at 75 rpm. **Figure S1.** Mean (standard deviation) plasma concentrations of vericiguat (µg/L) after a single dose of vericiguat (intact tablet 10 mg) followed by a single 30-min intravenous infusion of 20 µg 14C-labeled vericiguat starting 4 h after oral vericiguat dosing (n = 10). **Figure S2.** Individual plasma concentrations of vericiguat (µg/L) after a single dose of vericiguat (intact tablet 10 mg) followed by a single 30-min intravenous infusion of 20 µg 14C-labeled vericiguat starting 4 h after oral vericiguat dosing (n = 10). **Figure S3.** Mean (standard deviation) plasma concentrations of vericiguat (µg/L) (dose normalized) after a single dose of vericiguat (intact tablet [fed and fasted] and PEG solution [fasted]), n = 15. **Figure S4.** Individual plasma concentrations of vericiguat (µg/L) after a single dose of vericiguat (n = 15) (A) 1.25 mg intact tablet fasted, (B) 5 mg intact tablet fasted, (C) 5 mg PEG solution fasted, (D) 5 mg intact tablet fed. **Figure S5.** Mean (standard deviation) plasma concentrations of vericiguat (µg/L) after a single dose of vericiguat (intact tablets [fed], n = 13). **Figure S6.** Individual plasma concentrations of vericiguat (µg/L) after a single dose of vericiguat (intact tablets [fed and fasted], n = 13). (A) 1.25 mg intact tablet fed, (B) 2.5 mg intact tablet fed, (C) 5 mg intact tablet fed, (D) 10 mg intact tablet fed. **Figure S7.** Mean (standard deviation) plasma concentrations of vericiguat (µg/L) after a single dose of vericiguat (intact tablet [fed and fasted], n = 29). **Figure S8.** Individual plasma concentrations of vericiguat (µg/L) after a single dose of vericiguat (A) 2.5 mg fed, (B) 5 mg fed, (C) 10 mg fed, (D) 10 mg fasted. **Figure S9.** Mean plasma concentrations of vericiguat (µg/L) after a single dose of vericiguat (intact tablet and crushed tablet, n = 29). **Figure S10.** Individual plasma concentrations of vericiguat (µg/L) after a single dose of vericiguat 10 mg (intact tablet and crushed tablet formulations, n = 29) (A) crushed tablet high-fat, high-calorie meal, (B) intact tablet high-fat, high-calorie meal, (C) intact tablet low-fat, low-calorie meal.

Acknowledgements

The authors would like to thank the healthy subjects and study site personnel involved in these studies. Medical writing support was provided by Laila Guzadhur, PhD, of Scion, London, UK, supported by Bayer and Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA according to Good Publication Practice guidelines (https://www.acpjournals.org/doi/10.7326/M15-0288). The Sponsor was involved in the study design, collection, analysis, and interpretation of data, as well as data checking of information provided in the manuscript. However, ultimate responsibility for opinions, conclusions and data interpretation lies with the authors.

Clinical trial registry data

Trial identifier	Registry	FSFV	LSLV
2011–004841-42	EudraCT	16 December 2011	30 March 2012
2012–004839-23	EudraCT	08 January 2013	13 February 2013
2015–001568-20	EudraCT	07 October 2015	28 October 2015
2016–000980-18	EudraCT	21 June 2016	13 October 2016
2016–005074-35	EudraCT	16 May 2017	29 August 2017
NCT03145038	ClinicalTrials.gov		

Authors' contributions

Substantial contributions to the conception or design of the work: CB, MB, UM, SL, ML, WM. Acquisition, analysis, or interpretation of data for the work: CB, MB, UM, SL, ML, WM. Drafting the work or revising it critically for important intellectual content: CB, MB, UM, SL, ML, WM. Final approval of the version to be published: CB, MB, UM, SL, ML, WM. Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved: CB, MB, UM, SL, ML, WM. All authors read and approved the final manuscript.

Funding

Funding for this research was provided by Bayer AG, Berlin, Germany, and Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA.

Declarations

Competing interests

W. Mueck, U. Muenster, and C. Becker are employees of Bayer AG and may own stock in the company. M. Lobmeyer and M. Boettcher are former employees of Bayer AG and may own stock in the company. S. Loewen is an employee of Chrestos Concept GmbH & Co. KG, which received funding for this analysis from Bayer AG.

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Received: 20 September 2021 Accepted: 26 September 2022
Published online: 01 November 2022

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