



Impact of fedratinib on the pharmacokinetics of transporter probe substrates using a cocktail approach

Ken Ogasawara¹ · Rebecca N. Wood-Horrall² · Mark Thomas¹ · Michael Thomas¹ · Liangang Liu¹ · Mary Liu¹ · Yongjun Xue¹ · Sekhar Surapaneni¹ · Leonidas N. Carayannopoulos¹ · Simon Zhou¹ · Maria Palmisano¹ · Gopal Krishna¹

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Abstract

Introduction Fedratinib, an oral, selective Janus kinase 2 inhibitor, has been shown to inhibit P-glycoprotein (P-gp), breast cancer resistance protein (BCRP), organic anion transporting polypeptide (OATP) 1B1, OATP1B3, organic cation transporter (OCT) 2, and multidrug and toxin extrusion (MATE) 1 and MATE2-K in vitro. The objective of this study was to evaluate the influence of fedratinib on the pharmacokinetics (PK) of digoxin (P-gp substrate), rosuvastatin (OATP1B1/1B3 and BCRP substrate), and metformin (OCT2 and MATE1/2-K substrate).

Methods In this nonrandomized, fixed-sequence, open-label study, 24 healthy adult participants received single oral doses of digoxin 0.25 mg, rosuvastatin 10 mg, and metformin 1000 mg administered as a drug cocktail (day 1, period 1). After a 6-day washout, participants received oral fedratinib 600 mg 1 h before the cocktail on day 7 (period 2). An oral glucose tolerance test (OGTT) was performed to determine possible influences of fedratinib on the antihyperglycemic effect of metformin.

Results Plasma exposure to the three probe drugs was generally comparable in the presence or absence of fedratinib. Reduced metformin renal clearance by 36% and slightly higher plasma glucose levels after OGTT were observed in the presence of fedratinib. Single oral doses of the cocktail ± fedratinib were generally well tolerated.

Conclusions These results suggest that fedratinib has minimal impact on the exposure of P-gp, BCRP, OATP1B1/1B3, OCT2, and MATE1/2-K substrates. Since renal clearance of metformin was decreased in the presence of fedratinib, caution should be exercised in using coadministered drugs that are renally excreted via OCT2 and MATEs.

Trial registration Clinicaltrials.gov NCT04231435 on January 18, 2020.

Keywords Fedratinib · Drug–drug interaction · Transporter · Digoxin · Rosuvastatin · Metformin

Introduction

Fedratinib is an oral, selective inhibitor of wild-type and mutationally activated Janus kinase (JAK) 2 and FMS-like tyrosine kinase 3. The JAK/signal transducer and activation of transcription (STAT) pathway is involved in cytokine signaling, and dysregulation of this pathway may play a role in hematologic malignancies [1, 2]. Fedratinib inhibits dysregulated JAK2 signaling that drives the pathogenesis of myeloproliferative neoplasms, including myelofibrosis (MF)

[3]. Previous studies have demonstrated that, in addition to having a manageable safety profile, fedratinib significantly reduced splenomegaly, normalized peripheral cell counts, including leukocytes and platelets, and improved symptom burden in patients with MF [4]. In 2019, fedratinib was approved for the treatment of adult patients with intermediate-2 or high-risk primary or secondary MF by the US Food and Drug Administration (FDA) [5].

Patients with MF have a mean age of 61–66 years [6], and a majority have comorbidities of which the most common are cardiovascular disease, diabetes, hypertension, liver disease, and previous solid tumors [7–9]. Because of these comorbidities, patients with MF frequently take several medications concomitantly with treatment for their hematologic disease—making characterization of potential fedratinib drug–drug interactions (DDI) particularly

✉ Ken Ogasawara
ken.ogasawara@bms.com

¹ Bristol Myers Squibb, Summit, NJ, USA

² PPD Development LP, Austin, TX, USA

important. Fedratinib is metabolized by cytochrome P450 (CYP) enzymes, predominantly by CYP3A4 [10, 11], and concomitant administration of fedratinib with strong CYP3A4 inhibitors significantly increased fedratinib exposure [12]. Fedratinib inhibits several CYP enzymes, including CYP3A4, and fedratinib treatment can result in increased plasma levels of other drugs metabolized by CYP3A4 and other CYP enzymes [10, 13].

Along with drug-metabolizing enzymes, cell membrane transporter proteins involved in tissue uptake and excretion of small molecules also frequently influence drug pharmacokinetics (PK) and pharmacodynamics (PD) in a clinically relevant fashion [14–16]. Transporters often involved in DDI include P-glycoprotein (P-gp), breast cancer resistance protein (BCRP), organic anion transporting polypeptide (OATP) 1B1, OATP1B3, organic cation transporter (OCT) 2, and multidrug and toxin extrusion (MATE) 1 and MATE2-K [15].

Fedratinib has been shown to inhibit P-gp, BCRP, OATP1B1/1B3, OCT2, and MATE1/2-K in vitro [5, 13]; thus, a clinical investigation of the transporter-mediated DDI potential was performed. The primary objective of this study was to evaluate the influence of fedratinib on the PK of probe substrates of these transporters, including digoxin, a substrate of P-gp; rosuvastatin, a substrate of OATP1B1/1B3 and BCRP; and metformin, a substrate of OCT2 and MATE1/2-K. In addition, the impact of fedratinib on metformin-mediated antihyperglycemic effects was evaluated using an oral glucose tolerance test (OGTT) [17, 18]. The secondary objective was to evaluate the safety and tolerability of fedratinib coadministration with digoxin, rosuvastatin, and metformin in healthy adult participants.

Materials and methods

Study and ethical considerations

This was a nonrandomized, open-label study in healthy adult participants. The protocol complied with recommendations of the 18th World Health Congress (Helsinki, 1964) and all applicable amendments. The protocol and its amendment were submitted to an institutional review board (Salus Independent Review Board, Austin, TX) for review and written approval. Written informed consent was obtained prior to the conduct of any study-related procedures.

Study population

Healthy adult male and female participants between 18 and 65 years of age who had a body mass index ≥ 18 and ≤ 33 kg/m² were enrolled. Participants were considered healthy based on medical history, physical examination,

clinical laboratory tests, vital signs, and 12-lead electrocardiogram (ECG), with supine systolic blood pressure ≥ 90 and ≤ 140 mmHg, supine diastolic blood pressure ≥ 50 and ≤ 90 mmHg, and pulse rate ≥ 45 and ≤ 100 beats per minute at screening. Conducting the study in healthy adult participants mitigated the potential confounding effects of the hematologic disease state, comorbidities, and concomitant medications, and obviated the significant enrollment challenges associated with performing the study in patients with MF.

Study design and treatment

In this nonrandomized, fixed-sequence, open-label study (NCT04231435), the study duration was approximately 8 weeks from screening through the follow-up telephone call (Supplementary Fig S1). On day 1 (period 1), participants were administered a cocktail of single doses of digoxin (1 \times 0.25-mg tablet), rosuvastatin (1 \times 10-mg tablet), and metformin (1 \times 1000-mg tablet). Based on the terminal elimination half-life ($t_{1/2}$) of the probe drugs [19–21], a 6-day washout was considered sufficient to prevent carryover to the second dose of probe drugs. After the 6-day washout period, participants received fedratinib (6 \times 100-mg capsules) 1 h before a cocktail of digoxin (1 \times 0.25-mg tablet), rosuvastatin (1 \times 10-mg tablet), and metformin (1 \times 1000-mg tablet) on day 7 (period 2). For the OGTT, a glucose dose of 75 g was administered orally 2 h after the oral administration of the digoxin, rosuvastatin, and metformin cocktail. The antiemetic palonosetron (0.25 mg) was administered as a 30-s intravenous infusion approximately 30 min before fedratinib administration on day 7 (period 2) to reduce the potential for fedratinib-related nausea and vomiting. Palonosetron was also administered approximately 90 min before digoxin, metformin, and rosuvastatin administration on day 1 (period 1) to ensure similar conditions of probe drug administration in each study period. Palonosetron was selected because its DDI profile made unlikely any confounding PK interactions with the probe drugs [22, 23], while its intravenous route of administration avoided potential physical absorption effects on the probe drugs in the lumen of the digestive tract. Participants were discharged from the clinical site on day 22 and received a follow-up telephone call within 2 to 5 days of discharge.

PK and PD sampling times and bioanalytical methods

Blood samples were collected for measurement of plasma digoxin, rosuvastatin, and metformin concentrations on days 1 and 7 before dosing, and 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 48, 72, and 96 h post dose of the digoxin, rosuvastatin, and metformin cocktail. To measure fedratinib plasma

concentrations, blood samples were collected predose, at 0.5 h post dose of fedratinib, and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 48, 72, 96, 120, 168, and 192 h post dose of the digoxin, rosuvastatin, and metformin cocktail. To determine urine metformin concentrations, urine samples were collected before dosing and at 0–2, 2–4, 4–6, 6–8, 8–12, 12–24, and 24–48 h post dose of the digoxin, rosuvastatin, and metformin cocktail. Blood samples were collected for measurement of plasma glucose for OGTT before and at 15, 30, 45, 60, 90, 120, and 180 min after oral glucose administration.

Following liquid–liquid extraction for digoxin, supported-liquid extraction for rosuvastatin, or protein precipitation extraction for metformin, plasma concentrations of digoxin, rosuvastatin, and metformin were determined using validated reversed-phase liquid chromatography–tandem mass spectrometry (LC–MS/MS) assays with lower limit of quantitation (LLOQ; calibration range) of 0.05 (0.05–10) ng/mL, 0.02 (0.02–20) ng/mL, and 2 (2–2000) ng/mL, respectively (Covance Bioanalytical Services, LLC, Indianapolis, IN). Intraday precision values were $\leq 8.0\%$ for digoxin, $\leq 7.7\%$ for rosuvastatin, and $\leq 4.4\%$ for metformin. Interday precision values were $\leq 4.7\%$ for digoxin, $\leq 6.0\%$ for rosuvastatin, and $\leq 5.2\%$ for metformin. Interday accuracy values were within $\pm 3.3\%$ for digoxin, within $\pm 4.8\%$ for rosuvastatin, and within $\pm 4.5\%$ for metformin. Plasma fedratinib concentrations were determined using a validated LC–MS/MS assay [10, 24]. Following a dilution procedure for metformin, urine concentrations of metformin were determined using a validated reversed-phase LC–MS/MS assay with LLOQ (calibration range) of 5 (5–2500) $\mu\text{g/mL}$ (WuXi AppTec, Plainsboro, NJ). The intraday precision, interday precision, and interday accuracy values were $\leq 9.96\%$, $\leq 7.09\%$, and within $\pm 10.5\%$, respectively.

PK variables

PK parameters were estimated for digoxin, rosuvastatin, metformin, and, when applicable, fedratinib. Plasma PK parameters included maximum observed plasma concentration (C_{max}), time to C_{max} (t_{max}), area under the plasma concentration–time curve (AUC) from time 0 to the last time point with a measurable concentration (AUC_{0-t}), AUC from time 0 to infinity ($\text{AUC}_{0-\infty}$), $t_{1/2}$, apparent total plasma clearance, and apparent total volume of distribution during the terminal phase. Urinary PK parameters for metformin included total amount excreted in the urine, percentage of metformin excreted in the urine, and renal clearance (CL_r).

Statistical methods

Approximately 24 participants were planned to be enrolled so that ≥ 12 participants would complete the study. An analysis of variance model with treatment as a fixed effect

and participant as a random effect was performed separately for each comparison on the natural log-transformed C_{max} , AUCs, and CL_r (metformin only). The geometric means along with ratios of the geometric means (expressed as a percentage) and associated 90% CIs were presented for digoxin, rosuvastatin, and metformin plus fedratinib (“cocktail + fedratinib,” test) versus digoxin, rosuvastatin, and metformin alone (“cocktail,” reference). For t_{max} , the Wilcoxon signed-rank test, Hodges–Lehmann estimate, and 90% CIs were calculated for the median difference between treatments.

Safety assessment

Safety was monitored throughout the study. Safety assessments included treatment-emergent adverse events (TEAEs), physical examinations, vital sign measurements, 12-lead ECG, glucose level measurements (via finger sticks) as clinically indicated, and clinical laboratory information (eg, hematology, chemistry, urinalysis). TEAEs were recorded from the time of consent form signing to study completion and up to 30 days after the last dose.

Results

Participants and participant disposition

A total of 24 healthy adults were enrolled, and 22 of those participants completed the study. Two participants (8.3%) discontinued; both discontinued prior to dosing with fedratinib, and neither discontinuation was considered related to study treatment. One participant discontinued on day 7 due to a diagnosis of trichomoniasis and the need for that infection to be treated with metronidazole. The second participant was found to have frequent premature atrial contractions on predose ECG (and subsequent rhythm strip) on day 7. This was considered not clinically significant (and no adverse event was reported), but the participant did not receive planned study treatment on day 7 and discontinued from the study on day 8 (due to investigator’s discretion). All 24 enrolled participants were included in the safety, PK, and PD populations, but the two discontinued participants provided data for period 1 only.

Demographics and baseline characteristics are shown in Table 1. Overall, 15 (62.5%) participants were male and 9 (37.5%) were female, with a mean age of 34 years (20–61). There were 13 (54.2%) White, 10 (41.7%) Black or African American, and 1 (4.2%) Asian participants.

Table 1 Demographic and baseline characteristics

| Parameter | Overall (N=24) |
|--|---------------------|
| Age, mean (range), years | 33.8 (20–61) |
| Height, mean (range), cm | 171.3 (152.0–195.5) |
| Weight, mean (range), kg | 82.0 (49.7–120.4) |
| Body mass index, mean (range), kg/m ² | 27.8 (20.2–32.9) |
| Sex, n (%) | |
| Male | 15 (62.5) |
| Female | 9 (37.5) |
| Race, n (%) | |
| Black or African American | 10 (41.7) |
| White | 13 (54.2) |
| Asian | 1 (4.2) |
| Ethnicity, n (%) | |
| Hispanic or Latino | 8 (33.3) |
| Not Hispanic or Latino | 16 (66.7) |

Influence of fedratinib on digoxin, rosuvastatin, and metformin plasma PK

Mean plasma concentration–time profiles of digoxin, rosuvastatin, metformin, and fedratinib following single oral administration of the drug cocktail in period 1 and single oral administration of the cocktail + fedratinib 600 mg in period 2 are presented on linear and semilogarithmic scales in Fig. 1a–d. Following single oral doses of the cocktail, all three probe drugs exhibited a rapid absorption phase followed by a biphasic elimination phase with plasma concentrations measurable, on average, up to at least 72 h post dose. Following a single oral dose of the probe drug cocktail in the presence of fedratinib, concentrations of the probe drugs were generally comparable to that observed in the absence of fedratinib. PK parameters (geometric mean and geometric percent coefficient of variation [CV%]) are shown in Table 2.

Geometric mean digoxin plasma exposures when the cocktail was administered with fedratinib were approximately 99%, 103%, and 111% for C_{\max} , AUC_{0-t} , and $AUC_{0-\infty}$, respectively, of that when the cocktail was administered alone (Table 3). The 90% CI of the ratio of geometric means (cocktail + fedratinib/cocktail) lay within customary bioequivalence limits (80–125%) for all PK parameters. A statistically significant delay was observed in median t_{\max} in the presence of fedratinib (1.92 h) compared with t_{\max} in the absence of fedratinib (1.50 h) ($P=0.0162$).

Geometric mean rosuvastatin plasma exposures when the cocktail was administered with fedratinib were approximately 80%, 101%, and 102%, for C_{\max} , AUC_{0-t} , and $AUC_{0-\infty}$, respectively, of that when the cocktail was administered alone (Table 3). The 90% CI of the ratio of geometric means (cocktail + fedratinib/cocktail) lay within customary

bioequivalence limits for AUC_{0-t} and $AUC_{0-\infty}$. Furthermore, t_{\max} for rosuvastatin was comparable in the presence or absence of fedratinib ($P=0.0552$).

Geometric mean metformin plasma exposures when the cocktail was administered with fedratinib were approximately 88%, 100%, and 97%, for C_{\max} , AUC_{0-t} , and $AUC_{0-\infty}$, respectively, of that when the cocktail was administered alone (Table 3). The 90% CI of the ratio of geometric means (cocktail + fedratinib/cocktail) lay within customary bioequivalence limits for AUC_{0-t} and $AUC_{0-\infty}$. Furthermore, t_{\max} for metformin was comparable in the presence or absence of fedratinib ($P=0.0693$).

Influence of fedratinib on metformin urinary elimination

When the drug cocktail was administered alone, the geometric mean (geometric CV%) total amount of metformin excreted in the urine up to 48 h post dose was 324 mg (28%), or 32.4% of the total dose, whereas in the presence of cocktail + fedratinib, the amount excreted was 204 mg (30%), or 20.4% of the total dose. In the presence of cocktail + fedratinib, metformin CL_r was significantly reduced by 35.8% despite no clinically relevant change in plasma metformin exposure (Table 3). The mean cumulative amount of metformin eliminated in urine is shown in Fig. 2.

Influence of fedratinib on antihyperglycemic effect of metformin

The metformin-mediated antihyperglycemic effects were evaluated by OGTT. Following a single dose of glucose in the absence and presence of fedratinib, plasma glucose concentrations gradually increased and returned to the baseline level over the 3-h observation period (Fig. 3). Both absolute and baseline-adjusted plasma glucose levels were higher in the presence of the cocktail + fedratinib from 0.75 h (after glucose administration) onward compared with cocktail alone. A small increase was seen in geometric mean (geometric CV%) absolute glucose AUC_{0-3} (17% higher) in the presence of cocktail + fedratinib vs in the presence of the cocktail alone (357 h × mg/dL [16.3%] vs 306 h × mg/dL [14.7%]), as shown in Supplementary Table S1.

Safety evaluation

Overall, 15 of 24 participants (62.5%) reported ≥ 1 TEAE: nine of 24 participants (37.5%) after receiving the cocktail and 10 of 22 participants (45.5%) receiving cocktail + fedratinib. The majority of TEAEs were mild in severity.

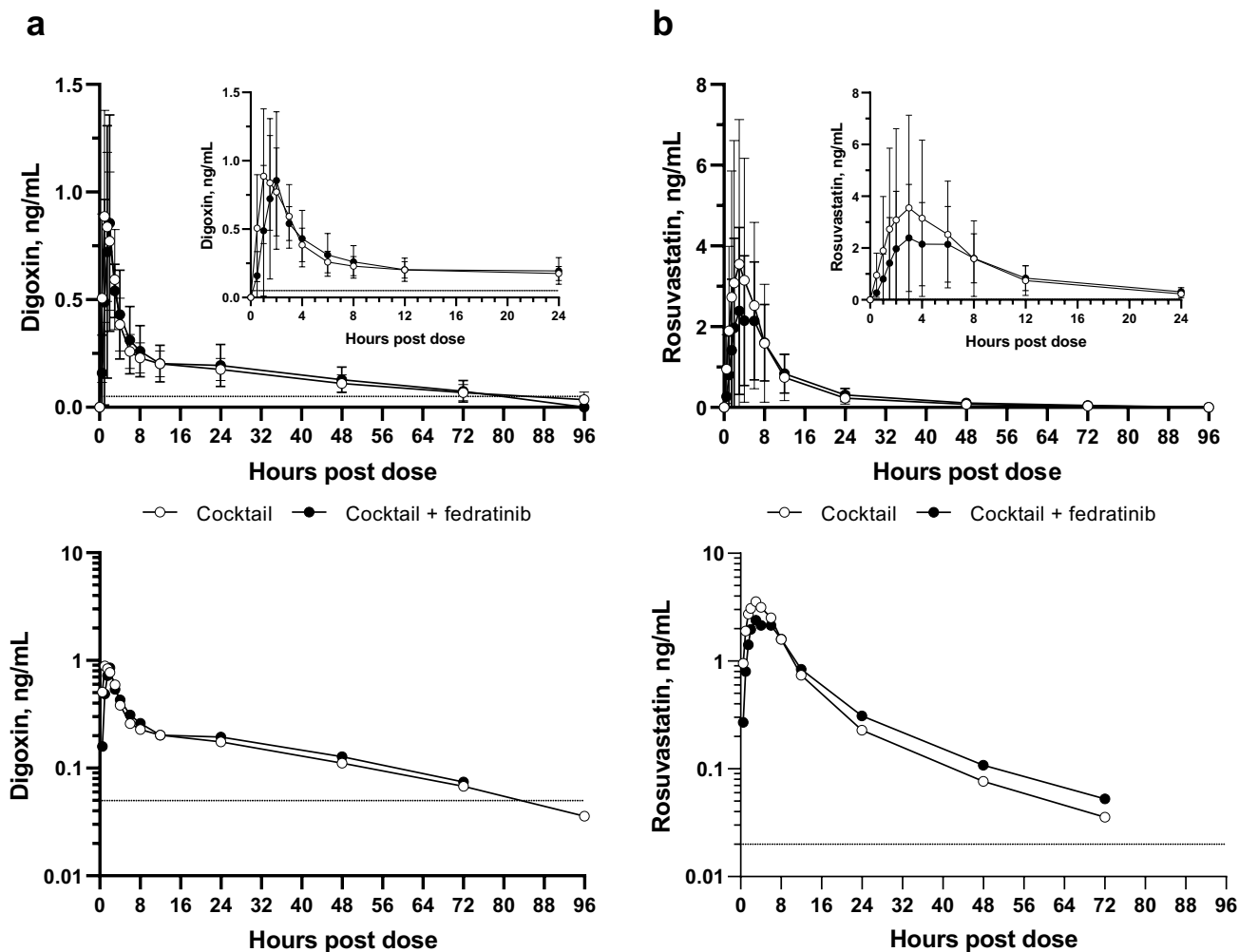


Fig. 1 Mean (\pm SD) plasma concentration–time profile of **a** digoxin, **b** rosuvastatin, **c** metformin, and **d** fedratinib following a single oral cocktail dose of digoxin (0.25 mg), rosuvastatin (10 mg), and metformin (1000 mg) when administered alone (open symbols) and when administered with fedratinib (600 mg, closed symbols), presented

in linear (upper panel) and semilogarithmic (lower panel) scales. The dotted lines depict the lower limit of quantitation for digoxin (**a**; 0.0500 ng/mL), rosuvastatin (**b**; 0.0200 ng/mL), metformin (**c**; 2.00 ng/mL) and fedratinib (**d**; 1.00 ng/mL). Fedratinib was administered during the second experimental period on day 7 only

Moderate TEAEs (nausea, vomiting) were reported by two participants after they received the drug cocktail. No deaths or severe or serious AEs were reported. Overall, 10 of 24 participants (41.7%) reported ≥ 1 TEAE suspected of being related to any study drug, with the most common treatment-related AEs being diarrhea ($n=7$) and nausea ($n=6$). (Supplementary Table S2). All TEAEs resolved by the end of the study. No participant had a clinical laboratory, vital sign, or 12-lead ECG result that was reported as a TEAE.

Plasma creatinine was measured on day -1 and at 12 h post dose of the cocktail on day 1 (period 1) and day 7 (period 2)—all at approximately the same time of day. Mean plasma concentrations of creatinine on baseline (day -1), and post treatment on day 1 (12 h after dosing of cocktail) were similar (80.6 $\mu\text{mol/L}$ and 79.4 $\mu\text{mol/L}$, respectively) and within the normal range for men and women.

However, an increase from baseline was observed on day 7 (12 h after dosing of cocktail + fedratinib), and the mean value (94.9 $\mu\text{mol/L}$) was within the normal range for men (67–112 $\mu\text{mol/L}$) but above the normal range for women (50–88 $\mu\text{mol/L}$) (Supplementary Fig. S2).

Discussion

Fedratinib has inhibitory effects on multiple transporters in vitro, including P-gp, BCRP, OATP1B1, OATP1B3, OCT2, MATE1, and MATE2-K. The purpose of this study was to evaluate the influence of fedratinib on the PK of clinical probe substrates of these transporters (digoxin, rosuvastatin, and metformin), as well as the impact of fedratinib

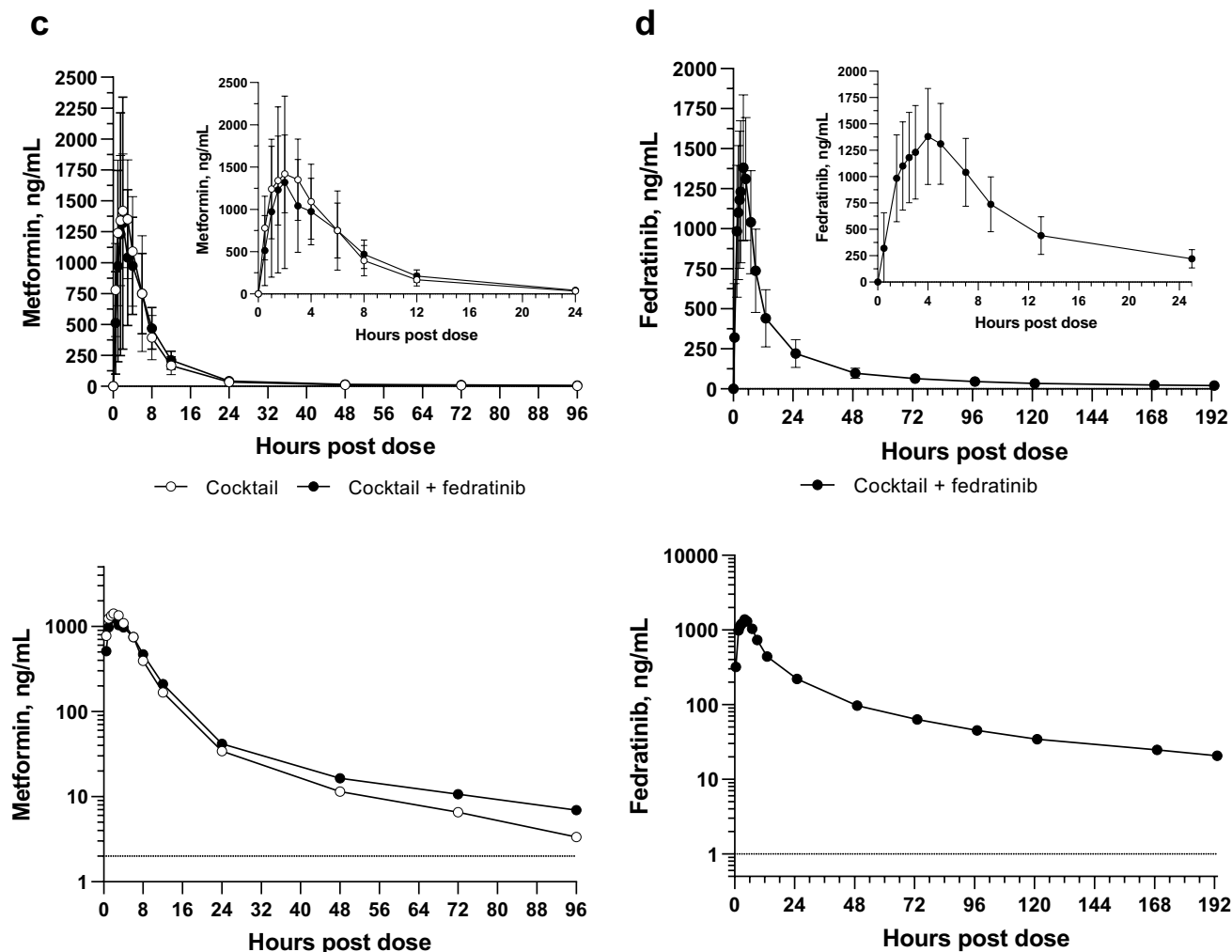


Fig. 1 (continued)

on metformin-mediated antihyperglycemic effects, with the goal of understanding the potential for transporter-mediated DDI with fedratinib in a clinical setting.

In vitro evaluations indicated that fedratinib inhibits P-gp (half-maximal inhibitory concentration [IC_{50}], 10.1 μ M), BCRP (IC_{50} , 29.9 μ M), OATP1B1 (IC_{50} , 16.4 μ M), OATP1B3 (IC_{50} , 9.51 μ M), OCT2 (IC_{50} , 0.78 μ M), MATE1 (IC_{50} , 0.352 μ M), and MATE-2 K (IC_{50} , 0.227 μ M) [13, 25]. Based on the FDA DDI guidance [16], fedratinib has the potential to inhibit P-gp and BCRP in vivo because the I_{gut}/IC_{50} value is ≥ 10 , where $I_{gut} = 400 \text{ mg}/250 \text{ mL} = 3050 \text{ }\mu\text{M}$ or 1.6 mg/mL, where I_{gut} is the intestinal luminal concentration of the interacting drug calculated as the dose/250 mL. Fedratinib also has the potential to inhibit OCT2, MATE1, and MATE2-K in vivo because the $I_{max,u}/IC_{50}$ value is ≥ 0.1 , where $I_{max,u} = 0.171 \text{ }\mu\text{M}$ (I_{max} [3.8 μ M or 2000 ng/mL] $\times f_{u,p}$ [0.045]), where $I_{max,u}$ is the maximal unbound plasma concentration of the interacting drug at steady state, I_{max} is the

maximal plasma concentration of the interacting drug at steady state, and $f_{u,p}$ is the fraction unbound in the plasma. R values for OATP1B1 and OATP1B3 were close to 1.1, where $R = 1 + (f_{u,p} [0.045] \times I_{in,max} [27 \text{ }\mu\text{M}]) / IC_{50}$, where $I_{in,max}$ is the estimated maximum plasma inhibitor concentration at the inlet to the liver. Thus, this study was designed to evaluate the influence of fedratinib on the PK of clinical probe substrates for these transporters. Key design considerations included choice and administration (i.e., as a cocktail) of probe drugs, duration of washout period, and fedratinib dose.

The probe drugs chosen in this study were digoxin (P-gp substrate), rosuvastatin (OATP1B1/OATP1B3 and BCRP substrate), and metformin (OCT2 and MATE1/2-K substrate), each of which is a prototypic clinical substrate for transporters according to the FDA [26]. Utility of these probe drugs administered together as a cocktail has been previously demonstrated [27, 28]—supporting use of the cocktail as a screening tool in an initial drug interaction

Table 2 Plasma PK parameters of digoxin, rosuvastatin, metformin, and fedratinib

| Analyte | PK parameter geometric mean (geometric CV%) [<i>n</i>] | Cocktail <i>N</i> =24 | Cocktail + fedratinib <i>N</i> =22 |
|--------------|--|--------------------------|---------------------------------------|
| Digoxin | AUC _{0–<i>t</i>} (h × ng/mL) | 12.2 (46) [24] | 12.4 (52) [22] |
| | AUC _{0–∞} (h × ng/mL) | 20.0 (14) [7] | 22.1 (30) [7] |
| | <i>C</i> _{max} (ng/mL) | 0.944 (52) [24] | 0.928 (46) [22] |
| | <i>t</i> _{max} ^a (h) | 1.50 (0.50–4.00) [24] | 1.92 (1.00–4.00) [22] |
| | <i>t</i> _{1/2} (h) | 40.6 (20) [23] | 42.1 (24) [20] |
| | CL/F (L/h) | 12.5 (14) [7] | 11.3 (30) [7] |
| | Vz/F (L) | 647 (13) [7] | 553 (27) [7] |
| Rosuvastatin | AUC _{0–<i>t</i>} (h × ng/mL) | 29.5 (65) [24] | 29.1 (58) [22] |
| | AUC _{0–∞} (h × ng/mL) | 30.7 (66) [22] | 30.6 (58) [22] |
| | <i>C</i> _{max} (ng/mL) | 2.89 (77) [24] | 2.24 (63) [22] |
| | <i>t</i> _{max} ^a (h) | 3.00 (1.50–6.00) [24] | 3.51 (1.92–8.00) [22] |
| | <i>t</i> _{1/2} (h) | 17.2 (76) [23] | 20.9 (52) [22] |
| | CL/F (L/h) | 325 (66) [22] | 327 (58) [22] |
| | Vz/F (L) | 7490 (65) [22] | 9840 (52) [22] |
| Metformin | AUC _{0–48} (h × ng/mL) | 10,000 (31) [24] | 9820 (37) [22] |
| | AUC _{0–<i>t</i>} (h × ng/mL) | 10,400 (31) [24] | 10,300 (38) [22] |
| | AUC _{0–∞} (h × ng/mL) | 10,600 (31) [23] | 10,600 (43) [18] |
| | <i>C</i> _{max} (ng/mL) | 1490 (37) [24] | 1310 (61) [22] |
| | <i>t</i> _{max} ^a (h) | 1.92 (1.00–6.00) [24] | 1.92 (1.03–6.00) [22] |
| | <i>t</i> _{1/2} (h) | 19.9 (96) [24] | 28.6 (223) [21] |
| | CL/F (L/h) | 94.3 (31) [23] | 93.9 (43) [18] |
| Fedratinib | Vz/F (L) | 2460 (66) [23] | 2480 (60) [18] |
| | AUC _{0–<i>t</i>} (h × ng/mL) | – | 24,300 (35) [22] |
| | AUC _{0–∞} (h × ng/mL) | – | 27,200 (34) [22] |
| | <i>C</i> _{max} (ng/mL) | – | 1410 (32) [22] |
| | <i>t</i> _{max} ^a (h) | – | 4.00 (1.50–7.00) [22] |
| | <i>t</i> _{1/2} (h) | – | 96.1 (27) [22] |
| | CL/F (L/h) | – | 22.0 (34) [22] |
| | Vz/F (L) | – | 3060 (44) [22] |

AUC area under the plasma concentration–time curve, AUC_{0–∞} AUC from time zero to infinity, AUC_{0–*t*} AUC from time zero to the last time point with a measurable plasma concentration, AUC_{0–48} AUC from time zero to 48 h post dose, CL/F apparent total plasma clearance, *C*_{max} maximum observed plasma concentration, CV coefficient of variation, *N* number of participants in the treatment group, *n* number of participants with evaluable values, PK pharmacokinetic, *t*_{1/2} terminal elimination half-life, calculated as $([\ln 2]/\lambda z)$, only when a reliable estimate for λz could be obtained (regression coefficient ≥ 0.8), *t*_{max} time to *C*_{max}, Vz/F apparent total volume of distribution during terminal phase. Drug cocktail, digoxin 0.25 mg + rosuvastatin 10 mg + metformin 1000 mg. Fedratinib dosage = 600 mg

^aMedian (minimum, maximum). AUC_{0–∞}, CL/F, and Vz/F values have been excluded from the calculation of summary statistics where %AUC_{extrap} > 20%

study—with significant changes in bioavailability triggering more focused follow-up DDI investigation. Although increased systemic exposure of rosuvastatin has been observed after coadministration with clinically relevant doses of metformin (by up to 54% and 23% at 500 and 750 mg, respectively) in healthy participants [29, 30], the interaction between metformin and rosuvastatin should not confound the results of this study because metformin does not inhibit OATP1B1, OATP1B3, or BCRP [31, 32], where the potential interaction between fedratinib and rosuvastatin

could occur. The underlying mechanism for increased systemic exposure of rosuvastatin by metformin is unclear but it was indicated that metformin leads to an increase in rosuvastatin bioavailability rather than a change in systemic clearance of rosuvastatin [27]. Thus, DDI effect of fedratinib on rosuvastatin could be assessed. Moreover, both treatment arms had the same doses of rosuvastatin and metformin; therefore, one treatment arm serves as a control for another treatment arm, balancing out any potential interaction between these two agents. A 6-day washout period between

Table 3 Statistical comparison of pharmacokinetic parameters

| Analyte | PK parameter (unit) | Treatment | <i>n</i> | Geometric mean | Geometric means ratio, % | Geometric means ratio, 90% CI | Intra participant CV% |
|---------------------------------|---------------------------------|-----------------------|----------|----------------|--------------------------|-------------------------------|-----------------------|
| Digoxin | AUC _{0–t} (h × ng/mL) | Cocktail | 24 | 12.2 | 102.65 | (92.28–114.19) | 20.8 |
| | | Cocktail + fedratinib | 22 | 12.5 | | | |
| | AUC _{0–∞} (h × ng/mL) | Cocktail | 7 | 19.8 | 111.25 | (99.06–124.94) | 7.31 |
| | | Cocktail + fedratinib | 7 | 22.1 | | | |
| <i>C</i> _{max} (ng/mL) | Cocktail | 24 | 0.944 | 98.85 | (81.56–119.80) | 39.0 | |
| | Cocktail + fedratinib | 22 | 0.934 | | | | |
| Rosuvastatin | AUC _{0–t} (h × ng/mL) | Cocktail | 24 | 29.5 | 101.07 | (91.95–111.10) | 18.4 |
| | | Cocktail + fedratinib | 22 | 29.8 | | | |
| | AUC _{0–∞} (h × ng/mL) | Cocktail | 22 | 30.9 | 101.58 | (91.58–112.67) | 19.2 |
| | | Cocktail + fedratinib | 22 | 31.4 | | | |
| <i>C</i> _{max} (ng/mL) | Cocktail | 24 | 2.89 | 80.44 | (71.09–91.01) | 24.2 | |
| | Cocktail + fedratinib | 22 | 2.33 | | | | |
| Metformin | AUC _{0–t} (h × ng/mL) | Cocktail | 24 | 10,400 | 99.75 | (88.07–112.98) | 24.7 |
| | | Cocktail + fedratinib | 22 | 10,300 | | | |
| | AUC _{0–∞} (h × ng/mL) | Cocktail | 23 | 10,700 | 97.34 | (84.83–111.69) | 24.2 |
| | | Cocktail + fedratinib | 18 | 10,400 | | | |
| | <i>C</i> _{max} (ng/mL) | Cocktail | 24 | 1490 | 87.99 | (75.69–102.29) | 29.9 |
| | | Cocktail + fedratinib | 22 | 1310 | | | |
| CL _r (L/h) | Cocktail | 24 | 32.3 | 64.20 | (59.40–69.30) | 15.1 | |
| | Cocktail + fedratinib | 22 | 20.7 | | | | |

Cocktail = digoxin 0.25 mg + rosuvastatin 10 mg + metformin 1000 mg (day 1 [period 1]). Cocktail + fedratinib = fedratinib 600 mg + digoxin 0.25 mg + rosuvastatin 10 mg + metformin 1000 mg (day 7 [period 2]). Geometric means, ratios of geometric means, and 90% CIs of the ratio of geometric means are from an ANOVA model with treatment as fixed effect and participant as random effect on the natural log-transformed PK parameters. The ratio and 90% CI of the ratio are presented as a percentage. Intra-participant CV% = square root of (exp[MSE within participant of ANOVA] – 1) × 100, where MSE is the mean squared error. AUC_{0–∞} values have been excluded where %AUC_{extrap} was > 20%

ANOVA analysis of variance, AUC_{0–∞} area under the plasma concentration–time curve from time zero to infinity, AUC_{0–t} area under the plasma concentration–time curve from time zero to the last time point with a measurable plasma concentration, *C*_{max} maximum observed plasma concentration, CL_r renal clearance, CV coefficient of variation, *n* number of participants with evaluable values, PK pharmacokinetic

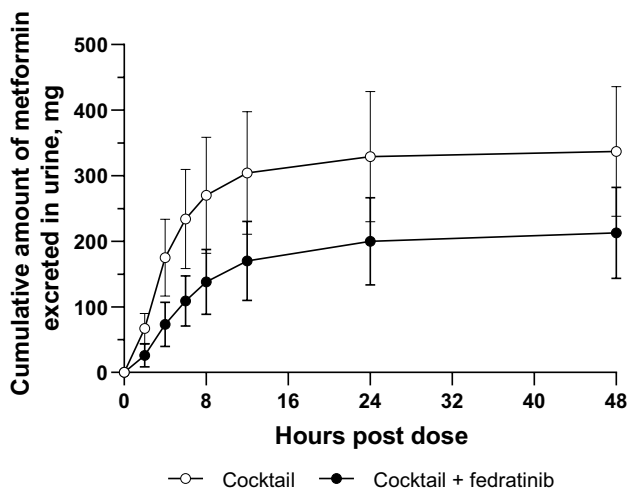


Fig. 2 Mean (\pm SD) cumulative amount of metformin excreted in urine following a single oral cocktail dose of digoxin 0.25 mg, rosuvastatin 10 mg, and metformin 1000 mg when administered alone (open symbols) and when administered with fedratinib 600 mg (closed symbols)

cocktail administrations was used in this study. Though this might be shorter than five times the upper range of published $t_{1/2}$ estimates for digoxin (26–45 h) [21], all predose plasma samples for digoxin as well as rosuvastatin and metformin in period 2 were below the LLOQ of their respective assays, validating the use of the 6-day washout period in this study.

The fedratinib dose to be administered prior to the cocktail in period 2 had to be chosen such that clinically relevant concentrations could be achieved in a single dose (no supportive multiple-dose experience having been available in healthy participants) in safe and tolerable fashion. Single fedratinib doses of up to 680 mg have been administered in healthy participants, with doses up to 500 mg having been generally well-tolerated [33]. Vomiting at 680 mg was considered a tolerability, rather than a safety, issue; thus, prophylaxis with an antiemetic was considered acceptable mitigation for fedratinib-related vomiting and nausea. Accordingly, 600 mg was chosen as the fedratinib dose in this study, with antiemetic prophylaxis, to maximize fedratinib exposure and tolerability. The *C*_{max} values at 600 mg were expected

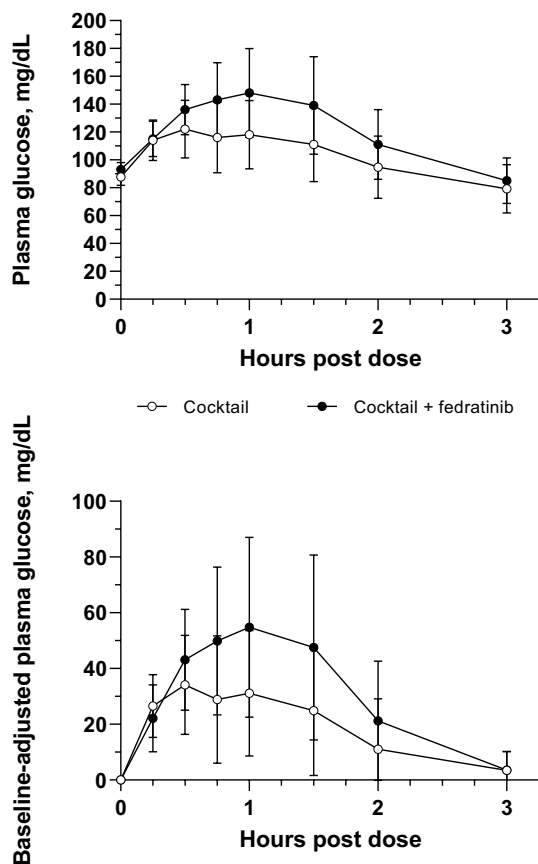


Fig. 3 Mean (\pm SD) plasma glucose concentration–time profiles by treatment. Baseline was defined as predose for each period and participant separately, i.e., period 1 (day 1) and period 2 (day 7) used predose records relative to that period (day). Absolute measured concentrations are shown in the upper panel. To estimate baseline-adjusted values, predose concentrations for each participant were subtracted from each postdose concentration; where baseline-adjusted concentrations were negative, they were set to zero

to provide concentrations higher than the IC_{50} values for OCT2 and MATE1/2-K, while the gut/portal concentrations at 600 mg are expected to be higher than those achieved with a clinically recommended 400-mg dose. Single oral doses of the drug cocktail components alone and coadministered with fedratinib were generally safe and well-tolerated by the healthy adults in this study. Most TEAEs reported were mild in severity. The primarily gastrointestinal findings associated with fedratinib administration in this study were consistent with previous reports from clinical trials [33, 34]. Palonosetron was chosen as a prophylactic antiemetic in this study instead of ondansetron, which has typically been used in clinical studies of fedratinib [35] because ondansetron is a potent inhibitor of MATE1 (K_i , 0.035 μ M) and MATE2-K (K_i , 0.015 μ M) in vitro [36] and decreased the renal clearance of metformin by 37% in healthy participants [37]. Palonosetron is also reported as an inhibitor of MATE1 (IC_{50} , 2.48 μ M) and MATE2-K (IC_{50} , 11.55 μ M) in vitro

[38]. However, the inhibitory potency of palonosetron on MATEs is weaker than those of ondansetron and fedratinib in vitro. Therefore, palonosetron is unlikely to have a significant impact on the influence on metformin renal clearance by fedratinib given that mean plasma palonosetron concentrations associated with the 0.25-mg intravenous dose fall well below its IC_{50} s for these transporters [39]. Furthermore, palonosetron was administered in both periods in this study (cocktail only and cocktail + fedratinib) such that any potential small effects on MATE1 and MATE2-K function would cancel out in the comparisons between periods.

Evaluation of the plasma PK parameters of digoxin (P-gp substrate), rosuvastatin (OATP1B1, OATP1B3, and BCRP substrate), and metformin (OCT2, MATE1, and MATE2-K substrate), generally suggested no clinically meaningful DDI, based on exposure in systemic circulation (plasma), between these probe drugs and fedratinib. Systemic plasma exposure to all 3 probe drugs was generally comparable after a single administration of the drug cocktail in the presence or absence of fedratinib. No apparent differences in dose-normalized C_{max} and AUCs of fedratinib were observed between this study (fedratinib 600 mg) and the recent study with CYP3A4 inducers (fedratinib 500 mg, [40]). However, a short but statistically significant delay in t_{max} was observed for digoxin in the presence of fedratinib (1.92 vs 1.50 h), which corresponds to lower digoxin concentrations in the presence of fedratinib in early hours after administration (0.5–1.5 h after digoxin administration) although digoxin concentrations showed higher interindividual variability in the early hours after administration than the later timepoints. This finding is not explained by P-gp inhibition, and exposure metrics of digoxin such as C_{max} and AUCs was comparable in the presence or absence of fedratinib. Wiebe et al. [41] recently reported that the effect of single-dose verapamil (a potent P-gp inhibitor) on digoxin systemic exposure was less than that expected from multiple-dose studies, suggesting that potential test compounds inhibiting P-gp could also be dosed attaining near steady-state concentration from a single dose before administering the cocktail. In this study, the impact of single-dose fedratinib on the PK of digoxin was investigated, however, 600 mg (1.5 times the clinically recommended dose) was used as fedratinib dose and no increase in digoxin exposure was observed in the presence of this higher than clinically recommended fedratinib dose while single-dose verapamil still had minor effect on digoxin exposure [41]. In addition, lower digoxin concentration in the presence of fedratinib in early hours after administration further confirms no P-gp inhibition by fedratinib since P-gp inhibition would be expected to have the opposite effect. Taken together, fedratinib is unlikely to inhibit P-gp in vivo at a clinical dose of 400 mg once daily.

Although no clinically meaningful DDI based on plasma PK for metformin was observed, a statistically significant

36% reduction in metformin CL_r was observed in the presence of fedratinib. Metformin is transported from the blood compartment into renal proximal tubular cells primarily by OCT2 [42]. MATE1 and MATE2-K are also involved in the efflux of metformin from renal proximal tubular cells to urine [43]. The combination of uptake by OCT2 and secretion by MATEs contributes to renal clearance of metformin. A decrease in metformin CL_r in the presence of fedratinib could thus be due to the inhibition of MATEs and OCT2 by fedratinib *in vivo*. The involvement of MATE2-K is less clear, as inhibition of MATE2-K by the selective MATE2-K inhibitor nizatidine had no effect on metformin CL_r [44]. It appears that equipotent inhibition of MATE1 and MATE2-K by fedratinib, unlike selective inhibition of MATE2-K by nizatidine, has translated into reduced CL_r of metformin in this study. This inhibition of OCT2 and MATEs by fedratinib appears to be consistent with a slight increase from baseline in plasma creatinine, another endogenous OCT and MATE substrate, observed 12 h after single administration of the cocktail + fedratinib, as has been observed for other drugs, such as trimethoprim, an inhibitor of OCT2 and MATEs [45]. One explanation for the lack of a clinically relevant impact of fedratinib on plasma metformin exposure could be that fedratinib inhibits renal secretion of metformin via MATEs but not uptake of metformin from blood into renal proximal tubular cells via OCT2 *in vivo*. Fedratinib has higher inhibition potencies against MATE1/2-K versus OCT2, which is consistent with other known inhibitors of OCT2 and MATEs [46]. Furthermore, the DDI between cationic drugs and cimetidine (an inhibitor of OCT2 and MATEs) at their clinical doses is suggested to be due to competitive inhibition of MATEs by cimetidine instead of OCT2 [47]. Inhibition of apical efflux transporters may result in increased intracellular drug concentrations in renal proximal tubular cells [48], which should be taken into consideration when fedratinib is administered in combination with potentially nephrotoxic drugs that are also OCT2 and MATE substrates.

In addition to fedratinib's effects on plasma and urinary metformin PK, its influence on the antihyperglycemic PD effect of metformin was also evaluated using an OGTT. The OGTT was included in both periods in which metformin was administered. Plasma glucose levels were higher in the presence of fedratinib (i.e., absolute glucose AUC_{0–3} was 17% higher). During the OGTT evaluation period (2–5 h after metformin administration), geometric mean plasma metformin concentrations were lower in the presence of fedratinib compared with the absence of fedratinib (at 2, 3, and 4 h post dose of metformin). The slight decrease in early metformin exposure by fedratinib might in part explain the slight decrease in antihyperglycemic PD effect of metformin after OGTT. A fedratinib-alone treatment period with the OGTT was not incorporated in this study because the phase

3 JAKARTA trial (in which patients with MF received placebo, fedratinib 400 mg, or fedratinib 500 mg once daily) demonstrated neither frequent adverse events of hyperglycemia, nor any adverse events of hypoglycemia, nor clinically meaningful changes from baseline in mean glucose levels in placebo or fedratinib dose groups (Bristol Myers Squibb, Data on file).

In conclusion, clinically meaningful influences of fedratinib on the plasma exposure of digoxin, rosuvastatin, and metformin were not observed. These results suggest that fedratinib has minimal impact on the exposure of P-gp, BCRP, OATP1B1/1B3, and OCT2/MATEs substrates. Since renal clearance of metformin was decreased in the presence of fedratinib, caution should be exercised for patients receiving fedratinib in combination with drugs that are renally excreted via OCT2 and MATEs.

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Author contributions KO and GK contributed to study design, data analysis, interpretation, and drafted manuscript. LNC, LL, and ML contributed to study design, data analysis, and interpretation. RNW-H and YX contributed to data acquisition and interpretation. MaT contributed to study design, data acquisition, and interpretation. MiT, SS, SZ, and MP contributed to study design and interpretation. All authors critically reviewed the draft manuscript and approved the final version to be published and agree to be accountable for all aspects of the work.

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Data availability Data requests may be submitted to Celgene, a Bristol Myers Squibb Company, at <https://vivli.org/ourmember/celgene/> and must include a description of the research proposal.

Declarations

Conflict of interest K.O., Ma.T., Mi.T., L.L., M.L., Y.X., S.S., L.N.C., S.Z., M.P., and G.K. are employees of, and hold equity ownership in, Bristol Myers Squibb. R.N.W–H. is an employee of PPD Development LP.

Ethics approval The protocol complied with recommendations of the 18th World Health Congress (Helsinki, 1964) and all applicable amendments. The protocol and its amendment were submitted to an institutional review board (Salus Independent Review Board, Austin, TX) for review and written approval.

Consent to participate Written informed consent was obtained prior to the conduct of any study-related procedures.

Consent for publication All authors critically reviewed the draft manuscript and approved the final version to be published and agree to be accountable for all aspects of the work.

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