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ORIGINAL ARTICLE

Midostaurin drug interaction profile: a comprehensive assessment of CYP3A, CYP2B6, and CYP2C8 drug substrates, and oral contraceptives in healthy participants

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Abstract

Purpose Midostaurin, approved for treating *FLT-3*-mutated acute myeloid leukemia and advanced systemic mastocytosis, is metabolized by cytochrome P450 (CYP) 3A4 to two major metabolites, and may inhibit and/or induce CYP3A, CYP2B6, and CYP2C8. Two studies investigated the impact of midostaurin on CYP substrate drugs and oral contraceptives in healthy participants.

Methods Using sentinel dosing for participants' safety, the effects of midostaurin at steady state following 25-day (Study 1) or 24-day (Study 2) dosing with 50 mg twice daily were evaluated on CYP substrates, midazolam (CYP3A4), bupropion (CYP2B6), and pioglitazone (CYP2C8) in Study 1; and monophasic oral contraceptives (containing ethinylestradiol [EES] and levonorgestrel [LVG]) in Study 2.

Results In Study 1, midostaurin resulted in a 10% increase in midazolam peak plasma concentrations (C_{max}), and 3–4% decrease in total exposures (AUC). Bupropion showed a 55% decrease in C_{max} and 48–49% decrease in AUCs. Pioglitazone showed a 10% decrease in C_{max} and 6% decrease in AUC. In Study 2, midostaurin resulted in a 26% increase in C_{max} and 7–10% increase in AUC of EES; and a 19% increase in C_{max} and 29–42% increase in AUC of LVG. Midostaurin 50 mg twice daily for 28 days ensured that steady-state concentrations of midostaurin and the active metabolites were achieved by the time of CYP substrate drugs or oral contraceptive dosing. No safety concerns were reported.

Conclusion Midostaurin neither inhibits nor induces CYP3A4 and CYP2C8, and weakly induces CYP2B6. Midostaurin at steady state has no clinically relevant PK interaction on hormonal contraceptives. All treatments were well tolerated.

Keywords Midostaurin · Drug–drug interaction · Midazolam · Bupropion · Pioglitazone · Oral contraceptive

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Introduction

The anti-leukemic agent midostaurin (Rydapt®) is a multi-targeted tyrosine kinase inhibitor that has been approved in more than 60 countries worldwide. It is used for the treatment of fms-related receptor tyrosine kinase 3 (*FLT-3*)-mutated acute myeloid leukemia (AML) in combination with daunorubicin and cytarabine at a dose of 50 mg twice daily. Midostaurin is also approved as a single agent at a dose of 100 mg twice daily for the treatment of advanced systemic mastocytosis (advSM) [1, 2].

Midostaurin is primarily metabolized by cytochrome P450 (CYP) 3A4 via oxidative pathways into two active metabolites, CGP62221 and CGP52421, which are in turn also metabolized by CYP3A4 [3]. In vitro studies indicated that midostaurin and its metabolites are reversible inhibitors and/or inducers of CYP3A, CYP2B6, and CYP2C8 [4]. Midostaurin and its two active metabolites showed time-dependent inhibition of CYP3A in vitro [3]. This interaction potential can affect the exposure of co-administered drugs, particularly those that are sensitive to CYP3A4, CYP2B6, or CYP2C8 substrates. The complex drug-drug interaction (DDI) profile of midostaurin and its metabolites can also affect their own metabolic clearance [4]. The net effect of auto-inhibition and auto-induction in vivo leans toward an auto-induction potential, as evidenced by the time-dependent kinetics, with a peak exposure during the first week of treatment, followed by a decline to steady-state after approximately 28 days [3, 4]. The median terminal half-lives ($T_{1/2}$) of midostaurin, CGP62221 and CGP52421 in plasma are approximately 20.3, 33.4, and 495 h, respectively [5]. Thus, due to the long half-life of CGP52421 and the time for midostaurin and CGP62221 to reach steady-state, a 28-day treatment period was considered necessary. Given the long terminal half-lives of midostaurin and its metabolites and the complex mixed DDI mechanism of midostaurin and its two active metabolites, it was important to evaluate DDI potential under steady-state conditions.

Midazolam (a sedative-hypnotic agent) [6], bupropion (an anti-depressant) [7], and pioglitazone (an antidiabetic agent) [8] are common medications and substrates of CYP3A [9, 10], CYP2B6 [10], and CYP2C8 [11], respectively. In Study 1, the impact of midostaurin on CYP3A and CYP2B6 was investigated with midazolam and bupropion as drug substrates in Arm 1 based on the Geneva cocktail [12]. There is no drug-drug interaction (DDI) between midazolam and bupropion, a two-drug substrates cocktail offers advantages such as reduced study duration and complexity. In Arm 2 of Study 1, the impact of midostaurin on CYP2C8 was investigated with pioglitazone as a single-dose drug substrate.

Monophasic oral contraceptives are commonly prescribed combinations, which contain ethinylestradiol (EES), an active estrogen component and levonorgestrel (LVG), a progesterone component and are mainly metabolized by the CYP3A enzyme.

A previous DDI study by Dutreix et al. reported the pharmacokinetic (PK) interactions of midostaurin with the CYP3A4 inhibitor ketoconazole, the CYP3A4 inducer rifampicin, and the CYP3A4 probe midazolam in three Phase I studies [13]. The study with a CYP3A4 substrate found no substantial changes to midazolam or its metabolite (1′-OH midazolam) exposure when comparing the PK profiles on day 3 vs. day 1. After multiple doses of midostaurin for 4 days, the midazolam exposure remained unchanged, and the 1′-OH midazolam area under the plasma concentration–time curve (AUC) was decreased by 24%. However, limited duration of midostaurin administration in that study did not allow conclusions on the long-term effects of midostaurin and its metabolites CGP62221 and CGP52421 on midazolam. Moreover, increasing the length of the treatment with midostaurin was not deemed feasible in healthy volunteers. This challenge was overcome by designing a stepwise approach by implementing a sentinel dosing using specific safety criteria and stopping rules to ensure safety in healthy participants receiving midostaurin over a longer (28 days) period of time in the current studies (see Methods).

A physiologically based pharmacokinetic (PBPK) model showed that predicted midazolam AUC ratio was > 0.5 and < 0.8 in the presence and absence of midostaurin, suggesting that it is a moderate inducer of CYP3A4 [9]. Additionally, a 1.9-fold increase in CYP3A activity of the endogenous biomarker 4β-hydroxycholesterol was observed, suggesting a weak-to-moderate induction by midostaurin at steady-state conditions [4]. Therefore, more data were required to fully understand the potential DDI of midostaurin with other drugs that are metabolized by CYP3A [13]. Additionally, using mechanistic static models [14], the overall effect (inhibition and/or induction) of midostaurin and its two active metabolites was evaluated. The AUC ratio of a victim drug in the presence and absence of midostaurin was predicted to be < 0.8 (the AUC ratio cut-off of 0.8 for induction) for CYP2B6 and CYP2C8 [data on file], suggesting midostaurin and its two metabolites could potentially induce these CYP enzymes in vivo.

Based on the PK and safety data observed in patients in the pivotal phase III (RATIFY) study, a modest 1.44- and 1.11-fold increase was observed in the exposure of midostaurin and CGP52421, respectively, with concomitant usage of strong CYP3A4 inhibitors, and no exposure increase was observed for CGP62221 [15]. No clinically relevant differences in safety were noted.

In the absence of supportive in vivo evidence, two clinical studies were conducted to investigate the impact of midostaurin at steady state following repeated twice daily oral doses of 50 mg midostaurin over 25 days on CYP substrates

(Study 1) and 24 days on oral contraceptives (Study 2). In Study 1, the impact of midostaurin and its two metabolites (CGP52421 and CGP62221) on CYP3A, CYP2B6, and CYP2C8 activity were investigated by evaluating the PK of specific substrates and their associated metabolites: CYP3A (midazolam and 1′-OH midazolam), CYP2B6 (bupropion and 4′-OH bupropion), and CYP2C8 (pioglitazone and hydroxy-pioglitazone). In Study 2, the impact of midostaurin and its two metabolites on the exposure of estrogen (EES) and progesterone (LVG) was investigated.

In addition, it was important to ensure that midostaurin at higher doses (100 mg twice daily is recommended in patients with advSM) did not impact the reliability of oral contraceptives. Due to safety concerns, it was not feasible to test higher doses of medications for an increased length of time in healthy participants. Therefore the results from Study 2 with oral contraceptives were extrapolated to midostaurin 100 mg twice daily dose using a PBPK model for midostaurin and its metabolites in healthy participants. Furthermore, the Novartis Global Safety Database (Argus) was searched to retrieve evidence on the prevalence of pregnancies and fetotoxicities in patients with AML and advSM, and the frequency of oral contraceptive use as concomitant or suspected comedication among patients with AML or advSM.

The studies also sought to evaluate the safety and tolerability of repeated oral doses of 50 mg twice daily midostaurin when co-administered with midazolam, bupropion, pioglitazone, or the oral contraceptive in healthy adult participants or healthy females with no childbearing potential, respectively. Furthermore, both studies assessed the PKs of midostaurin and its metabolites, CGP52421 and CGP62221, following repeated doses of midostaurin in the respective populations.

This publication reports the findings and insights regarding potential drug interactions and safety between midostaurin with CYP substrates and monophasic oral contraceptives, along with the PBPK analysis with oral contraceptives. Interpretation of these results and their implications for recommendations for the patient (labeling) are also discussed.

Materials and methods

Study designs and interventions

Study 1 with CYP substrates was a Phase 1, open-label, fixed-sequence DDI study in healthy adult participants. Participants were screened for eligibility and then admitted to the study center for baseline evaluation. There were two treatment arms—participants in Arm 1 received a single oral dose of 4 mg midazolam, 75 mg bupropion, and twice daily 50 mg midostaurin for 28 days; participants in Arm 2 received single oral dose of 30 mg pioglitazone and twice daily 50 mg midostaurin for 28 days. There were two treatment periods in each arm (Fig. 1).

During treatment Period 1 of each arm, a single oral dose of the cocktail drug substrates (midazolam and bupropion for Arm 1 and pioglitazone for Arm 2) was administered on day 1, and plasma concentrations of the drug substrate(s) and their respective metabolites were followed up to the morning of day 3 for midazolam (Arm 1) and until the morning of day 5 for bupropion (Arm 1) and pioglitazone (Arm 2). Treatment Period 1 was immediately followed by treatment Period 2. During treatment Period 2, participants in both Arms 1 and 2, received continuous treatment with midostaurin at 50 mg twice daily for 28 days (from day 5 to day 32). On day 29, participants received a single dose of the cocktail drug substrates (midazolam and bupropion for Arm 1 and pioglitazone for Arm 2) along with their morning dose of midostaurin. Plasma concentrations for midostaurin, its metabolites (CGP52421 and CGP62221), and the different drug substrates and their metabolites were then collected for 96 h until the morning of day 33. The participants continued to receive midostaurin until the evening of day 32, after which a final follow-up visit occurred 30 days after the last dose administration (day 62) for safety assessment.

Study 2 with oral contraceptives was a single-arm Phase 1, open-label, fixed-sequence DDI study in healthy female participants with no childbearing potential (Fig. 1). During Period 1, participants received a single dose of the oral contraceptive composed of 150 µg LVG and 30 µg EES and plasma concentrations were followed for 5 days. This period was immediately followed by Period 2. In Period 2, the participants received continuous treatment with midostaurin at 50 mg twice daily for 28 days (from day 6 to day 33). On day 29, the participants received a single dose of the oral contraceptive together with their morning dose of midostaurin.

PK sampling

Sequential PK sampling was conducted according to the assessment schedule for both studies. For Study 1 with CYP substrates, PK samples were collected at specified time points until 48 h post-dose for midazolam (pre-dose, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, and 48 h) and until 96 h for bupropion and pioglitazone (pre-dose, 0.5, 1, 2, 4, 6, 8, 12, 24, 48, 72, and 96 h). For both Arm 1 and Arm 2, midostaurin trough samples were collected prior to morning doses on days 6, 7, 14, 21, 28, 30, 31, 32 and 33; and the midostaurin PK profile on day 29 at 0, 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, and 12 h post-dose.

For Study 2 with oral contraceptives, trough PK samples were collected at pre-dose in the morning on days 7, 8, 14, 21, 28, 30, 31, 32, 33, and 34. PK samples for EES and LVG were collected on day 1 at pre-dose (0 h) and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 48, 72, 96, and 120 h post-dose.

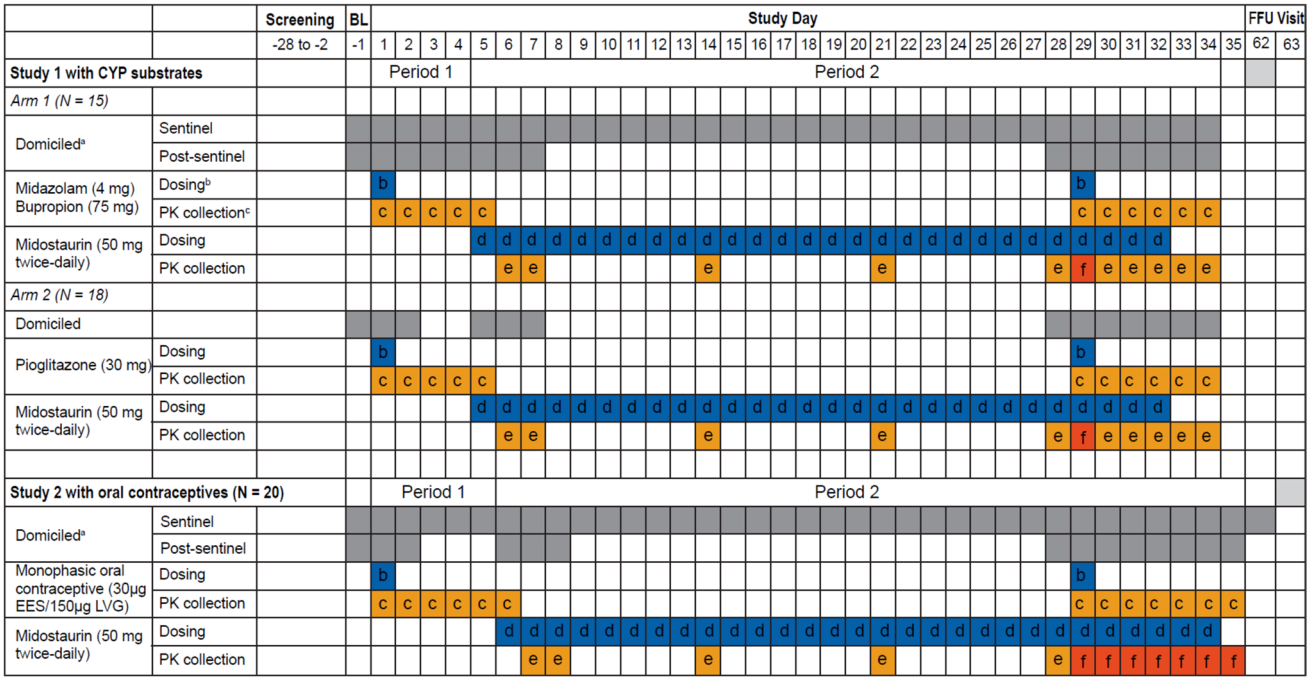

Fig. 1 Study 1 with CYP substrates and Study 2 with oral contraceptives. *BL* baseline, *D* day, *EES* ethinylestradiol, *FFU* final follow-up, *LVG* levonorgestrel, *OC* oral contraceptive, *PK* pharmacokinetic. [a]For Arm 1 only of Study 1: The participants were domiciled for the entire Period 1 and 2 (day − 1 to day 34) during sentinel dosing. Post-sentinel participants were domiciled from day − 1 to day 7 after morning dose of midostaurin and returned to the study center in the morning on day 8 to day 27 to take their morning dose of midostaurin supervised and were provided their evening dose to take at home. For Study 2: Participants were domiciled for the entire Period 1 and 2 during sentinel dosing (day − 1 to day 35). Post-sentinel subjects were domiciled from day − 1 to day 2, day 6 to day 8, and day 28 to day 34 of Period 1 and Period 2. They were provided their morning and evening dose of midostaurin supervised from days 28 to 33. [b]Single dose. [c]Full profile up to 48 h (midazolam), 96 h (bupropion and pioglitazone), and 120 h (monophasic oral contraceptives). [d]Twice daily. [e]Trough concentrations on days 7, 8, 14, 21, and 28 (in the morning). [f]PK profile

Serial samples for EES and LVG were collected on day 29 at pre-dose (0 h) and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24 (day 30), 48 (day 31), 72 (day 32), 96 (day 33), and 120 (day 34) hours post-dose. Midostaurin PK sampling was similar to that in Study 1.

Sentinel dosing

Both studies implemented a sentinel dosing approach to ensure the safety of the healthy participants receiving 50 mg twice daily midostaurin for 28 days (Fig. 1). The study initially enrolled three participants in the sentinel dosing cohort. These three participants were domiciled for the entire Period 1 and Period 2 of sentinel dosing. After the last dose of midostaurin, subjects remained in the study center for additional safety observation until 36 h post-dose, and a complete safety assessment was performed prior to discharge.

The study used specific safety criteria for guiding further enrollment, stopping the study, and/or progressing to post-sentinel dosing, including leukopenia or febrile neutropenia of Common Terminology Criteria for Adverse Events (CTCAE) Grade ≥ 3, aspartate aminotransferase (AST)/alanine aminotransferase (ALT) ≥ 3 times the upper limit of normal, or bilirubin ≥ 2 times the upper limit of normal. Detailed list is provided in the Online Resource 1.

Post-sentinel dosing

In Study 1 with CYP substrates, participants in Arm 1 were domiciled at the study center from day − 1 to day 7 (after third morning dose of midostaurin); and participants in Arm 2 were domiciled from day − 1 to day 2 and again from day 5 to day 7 (after third morning dose of midostaurin). During the out-participant period, they returned to the center for morning midostaurin dosing and received their evening dose to take at home. Safety checks were performed weekly. In Period 2, participants were domiciled from day 28 to day 33 (Arm 1 and Arm 2) and received a safety assessment prior to discharge. In Study 2 with oral contraceptives, participants were domiciled from day − 1 to day 2 of Period 1 and the first 2 days of Period 2 (day 6 to day 8) for PK sampling, dosing, and safety assessments. During the out-participant period, they returned to the center for morning midostaurin dosing and received their evening dose to take at home. In

Period 2, participants were domiciled from day 28 to day 34 and received a safety assessment prior to discharge. A final follow-up visit for a safety assessment occurred 30 days after the last dose administration, and the total study duration ranged from approximately 90 to 91 days.

Study participants

Study 1 with CYP substrates enrolled healthy adult male and female participants of non-childbearing potential, aged between 18 and 65 years (inclusive) with a body mass index (BMI) between 18.0 and 29.9 kg/m^2, and with no history of cardiac disease or significant electrocardiogram (ECG) abnormalities. Key exclusion criteria included a history of cardiac disease, history of prolonged QT-interval syndrome or cardiac disease, and contraindication or hypersensitivity to any drug or metabolites from a similar class as the study drug. Study 2 with oral contraceptives enrolled healthy female participants aged 18–65 years (inclusive), with non-childbearing potential, with a BMI between 18.0 and 29.9 kg/m^2, and with no history of arterial or venous thromboembolism. Participants were excluded if they were allergic to the study drug or its metabolic components or had a history of ECG abnormalities that included prolonged QT-interval syndrome or cardiac disease. Detailed inclusion and exclusion criteria for both the studies are available in Online Resource 2.

Outcome measures

The primary endpoint for Study 1 with CYP substrates and Study 2 with oral contraceptives was the derived PK parameters (non-compartmental analysis [NCA]) of a single dose of midazolam, bupropion, pioglitazone, and EES and LVG when administered alone and concomitantly with midostaurin, respectively. The primary parameters measured were C_{max}, AUC_{last}, and AUC_{inf}, while secondary parameters included T_{max}, CL/F, Vz/F, and $T_{1/2}$. Definitions for the measured PK parameters are provided in Online Resource 3. The secondary endpoints for both the studies were adverse events (AEs) based on the CTCAE grade (severity) and frequency, as well as other safety data such as (ECG) and laboratory parameters. The other secondary endpoint was midostaurin (multiple dose) and metabolite (CGP52421 and CGP62221) PK parameters $C_{max,ss}$, AUC_{tau} interval tau at steady-state, $T_{max,ss}$, CL/F, and Vz/F. The exploratory endpoint was PK parameters (NCA) of the drug substrate's metabolites when administered alone and concomitantly with midostaurin, including C_{max}, T_{max}, AUC_{last}, and metabolic ratios (Online Resource 3).

Statistical analysis

There were three population sets, the full analysis set (FAS), the safety analysis, set and the PK analysis sets (PASs). FAS and safety analysis set were identical in the studies. The PAS included all participants who provided an evaluable PK profile for at least one period. In Study 1, there were three PASs, one for probe drugs in each arm: midazolam and bupropion in Arm 1 (PAS1), pioglitazone in Arm 2 (PAS2), and one for midostaurin (PAS3). In Study 2, there were two PASs, one for oral contraceptive and the other for midostaurin.

Analysis of the primary PK parameters to estimate the effect of midostaurin (and its metabolites CGP62221 and CGP52421) on the PK of midazolam (and its metabolite 1′-hydroxy midazolam), bupropion (and its metabolite hydroxy-bupropion), pioglitazone (and its metabolite hydroxy-pioglitazone), and LVG and EES components of the oral contraceptives were done using a linear mixed model.

Geometric mean ratios of the PK parameters obtained in the treatment with the drug substrate + midostaurin were compared to those obtained in treatment with the drug substrate alone. Point estimates and two-sided 90% confidence interval (CI) for the difference between means of test and reference treatment (test-reference) were calculated, and were anti-log transformed to obtain geometric mean ratios. The median and the range of differences in the T_{max} values of midazolam, bupropion, and pioglitazone with 90% CI were calculated and presented for test versus reference.

Safety data were analyzed by number and percentage of participants with AEs and tabulated by system organ class (SOC) and preferred term (PT).

Physiologically based pharmacokinetic model

A PBPK model using Simcyp (Certara, L.P., Simcyp, Sheffield, UK) had been previously developed and verified to model the PK of midostaurin and its metabolites (CGP52421, and CGP6221) after 50 mg twice daily dosing in healthy volunteers [4]. The Sim-Healthy Volunteer population in Simcyp was used for further model refinement and qualification for PK and DDI predictions of midostaurin with midazolam using clinical data (Study 1 with CYP substrates) in the current analysis [15]. The model was applied to predict DDI with midazolam at high dose of midostaurin (100 mg twice daily). Additionally, the PBPK model was also used to qualify the DDI prediction of midostaurin (50 mg twice daily) with an oral contraceptive, eg., EES from clinical data (Study 2 with oral contraceptives) and then applied to predict the PK and DDI of multiple doses of midostaurin (100 mg twice daily), with EES.

Search strategy used in Novartis Global Safety Database (Argus)

To identify any post-marketing individual case report of potential DDI between concomitant hormonal contraceptives and midostaurin, a cumulative search until June 30, 2023, was conducted in the Novartis Global Safety Database (Argus) using the Medical Dictionary for Regulatory Activities (MedDRA; version 26.0) with SMQ (broad) pregnancy and neonatal topics. A second cumulative search was conducted until June 30, 2023, to retrieve all cases where the patient had taken midostaurin along with any of the oral contraceptives (estrogen, progestin, ethinylestradiol norgestrel or a combination of estrogen/progestin or ethinylestradiol/norgestrel) as concomitant/co-suspected medications.

Bioanalytical method

For Study 1 with CYP substrates, plasma concentrations of pioglitazone and hydroxy-pioglitazone was assessed using a validated LC–MS/MS method with a LLOQ of 0.500 ng/mL and 500 ng/mL, respectively (PRA Health Sciences Assen Netherlands). Concentrations of midazolam and 1′-hydroxy midazolam in plasma were measured using a validated LC–MS/MS method with a LLOQ of 0.100 ng/mL for midazolam and 100 ng/mL for 1′-hydroxy midazolam (PRA). Concentrations of bupropion and 1′-hydroxy bupropion in plasma samples was quantified by a validated LC-MS/MS method with a LLOQ of 0.5000 ng/mL and 250 ng/mL, respectively (PRA).

For Study 2 with oral contraceptives, concentrations of EES and LVG were measured in plasma with a LLOQ of 5.00 pg/mL and 500 pg/mL, respectively (SGS France).

For both Studies 1 and 2, the concentrations of midostaurin and its metabolites CGP52421 and CGP62221 in plasma were determined using a validated liquid chromatography-tandem mass spectrometry (LC–MS/MS) assay with a lower limit of quantitation (LLOQ) of 10 ng/mL (SGS France).

Results

Participant disposition

The Study 1 with CYP substrates enrolled 15 participants in Arm 1 and 18 in Arm 2. The median age was 58.0 years (43.0–65.0 years), and 48.5 years (28.0–64.0 years), for participants in Arm 1 and Arm 2, respectively. In Arm 2, two participants discontinued the study during treatment Period 2, due to AEs that resolved without sequelae. The Study with oral contraceptives enrolled 20 participants with a median age of 59.0 years (33.0–64.0 years). One participant discontinued the study during the treatment Period 1 (Online Resource 4).

All participants were of White race in both studies.

Pharmacokinetic results

DDI with midazolam, bupropion, and pioglitazone

The summaries of PK parameters of midazolam, bupropion and pioglitazone when administered alone and concomitantly with midostaurin are shown in Table 1 and Fig. 2A. In the presence of midostaurin 50 mg twice daily at steady-state, the mean peak plasma concentrations (C_{max}: geo-mean ratio [GMR] 1.10, 90% CI 0.95–1.28) of midazolam increased by 10%, while the total exposure AUCs (AUC_{last}: GMR 0.96, 90% CI 0.86–1.08 and AUC_{inf}: GMR 0.97, 90% CI 0.86–1.09) decreased by 4% and 3%, respectively (Table 2). Conversely, when midostaurin was co-administered with bupropion, the geometric mean peak plasma concentration (C_{max}: GMR 0.45, 90% CI 0.37–0.54) of bupropion decreased by 55% and total exposures AUCs (AUC_{last}: GMR 0.51, 90% CI 0.48–0.55; AUCinf: GMR 0.52, 90% CI 0.48–0.56) of bupropion decreased by 49% and 48%, respectively. Furthermore, when midostaurin was co-administered with pioglitazone, the mean peak plasma concentrations (C_{max}: GMR 0.90, 90% CI 0.78–1.03) of pioglitazone decreased by 10% and total exposures AUCs (AUC_{last}: GMR 0.94–90% CI 0.87, 1.00; AUC_{inf}: GMR 0.94, 90% CI 0.88–1.01) decreased by 6%.

Administration of a single oral dose of midazolam, bupropion, and pioglitazone, in the presence and absence of midostaurin (50 mg twice daily) at steady state, showed similar mean plasma concentrations for midazolam and pioglitazone, but lower plasma concentrations for bupropion in the presence of midostaurin. Midazolam and bupropion were quantifiable in all subjects up to 12 and 48 h post-dose, respectively, while pioglitazone was quantifiable up to 48 h post-dose in all participants. Figures showing PK profiles of probe drugs and midostaurin are presented in Online Resource 5.

The summaries of PK parameters of metabolite of midazolam (1'-OH midazolam), bupropion (1′-hydroxy-bupropion) and pioglitazone (hydroxy-pioglitazone) are shown in Online resource 6. Upon co-administration of midostaurin at steady-state, there was a decrease in the 1′-OH midazolam; geometric mean peak and total exposures by 23–25%. Geometric mean peak and total exposures of 1′-hydroxy-bupropion were decreased by 54% and 65%, respectively. Geometric mean peak exposures of hydroxy-pioglitazone increased by 5% in the presence of steady-state concentrations of midostaurin, while geometric mean total exposures of hydroxy-pioglitazone decreased by 4–7%.

Table 1 Summary statistics of plasma PK parameters of midazolam, bupropion, and pioglitazone (Study 1 with CYP substrates)

Treatment	C_{max} (ng/mL)	T_{max} (h)[a]	AUC_{last} (h*ng/mL)	AUC_{inf} (h*ng/mL)	$T_{1/2}$ (h)[a]	CL/F (L/h)	Vz/F (L)
Summary statistics of midazolam, and bupropion plasma PK parameter values in Study 1 with CYP substrates—Arm 1(PAS1)							
Midazolam (day 1) $N=15$	13.8 (6.85)	0.5 (0.48; 1.50)	50.6 (20.9)	53.6 (22.4)	6.59 (4.57; 8.00)	87.6 (36.8)	778 (265)
Midazolam + midostaurin (day 29) $N=15$	14.7 (4.78)	0.5 (0.48; 1.02)	47.7 (17.9)	50.7 (19.1)	6.84 (2.54; 10.2)	88.9 (32.7)	784 (217)
Bupropion (day 1) $N=15$	122 (60.4)	1 (0.48; 4.00)	490 (111)	515 (118)	20.6 (11.2; 36.6)	153 (36.9)	4900 (1690)
Midostaurin + bupropion (day 29) $N=15$	53.6 (24.6)	2 (0.50; 4.02)	248 (46.0)	264 (48.8)	13.5 (7.00; 26.6)	293 (53.4)	5930 (1690)
Summary statistics of pioglitazone plasma PK parameter values in Study 1 with CYP substrates—Arm 2 (PAS2)							
Pioglitazone (day 1) $N=16$	1040 (261)	2.02 (0.50; 4.05)	11,900 (4450)	11,900 (4440)	8.04 (4.72; 14.8)	2.84 (1.04)	34.4 (18.5)
Midostaurin + pioglitazone (day 29) $N=16$	962 (289)	2.02 (0.50; 4.02)	11,000 (3510)	11,000 (3460)	8.48 (4.38; 26.4)	2.95 (0.849)	49.5 (38.4)

Treatment	$C_{max,}$ss (ng/mL)	T_{max}, ss (h)[a]	AUC_{tau} (h*ng/mL)	C_{av}, ss (ng/mL)	$T_{1/2}$ (h)[a]	CL/F (L/h)	Vz/F (L)
Summary statistics of midostaurin plasma PK parameter values in Study 1 with CYP substrates—Arm 1 and Arm 2 (PAS3)							
Midostaurin + midazolam + Bupropion (day 29) $N=15$	907 (199)	1.5 (1.00; 4.00)	6500 (1490)	542 (124)	14.2 (7.46; 46.5) $n=9$	8.05 (1.73)	197 (144)
Midostaurin + pioglitazone (day 29) $N=16$	1090 (399)	1.24 (0.48; 4.02)	8290 (3610)	691 (301)	15.1 (8.26; 56.0) $n=14$	6.96 (2.46)	175 (109)

AUC area under the curve, *CL/F* clearance, C_{max} observed maximum plasma (or serum or blood) concentration following administration (mass/volume), *N* number of participants in respective treatment group, *n* number of subjects having respective non-missing, *PK* parameter value in respective treatment group, *PAS* Pharmacokinetic analysis set, *PK* pharmacokinetic, *ss* steady state, $T_{1/2}$ elimination half-life, T_{max} time to reach peak or maximum concentration, *Vz/F* apparent volume of distribution

[a]Values are mean (SD), except T_{max} and $T_{1/2}$ are median (min; max)

DDI with oral contraceptives

The summaries of PK parameters of the EES and LVG when administered alone and concomitantly with midostaurin are shown in Table 3 and Fig. 2B. In the presence of midostaurin 50 mg twice daily at steady state, the PKs of EES and LVG were assessed. For EES component, the geometric mean peak plasma concentrations, and total exposures of EES were slightly increased. The C_{max}: GMR 1.26, 90% CI 1.17–1.36 was increased by 26% and AUCs (AUC_{last}: GMR 1.10, 90% CI 1.01–1.21; AUC_{inf}: GMR 1.07, 90% CI 0.96–1.20) were increased by 7% and 10%. Similarly, in the presence of steady-state midostaurin concentrations, geometric mean peak plasma concentrations and total exposures of LVG component were slightly increased. The C_{max} (GMR 1.19, 90% CI 1.10–1.30) was increased by 19% and AUCs (AUC_{last}: GMR 1.42, 90% CI 1.31–1.53; and AUC_{inf}: GMR 1.29, 90% CI 1.19–1.41) were increased by 29–42%. Thus, there was no clinically significant PK DDI between multiple doses of midostaurin (50 mg twice daily) at steady-state and oral contraceptives containing EES and LVG in healthy females. As EES and LVG levels were not reduced by midostaurin, reliable contraception can thereby be maintained.

The trough plasma concentrations of midostaurin and its metabolites (CGP62221 and CGP52421) showed that PK steady state was achieved approximately after 2–3 weeks of twice daily dosing in both studies (Fig. 3A, B, C). The median $T_{1/2}$ for midostaurin in Study 1 with CYP substrates was 14.2 h and 15.1 h, in Arm 1 and Arm 2, respectively. The median $T_{1/2}$ for midostaurin in Study 2 with oral contraceptives was 8.29 h. The $T_{1/2}$ of CGP62221 in Study 1 with CYP substrates could only be reliably estimated for five participants in Arm 1, and 3 participants in Arm 2; median $T_{1/2}$ estimates were 38.6 h in Arm 1, and 49.9 h in Arm 2.

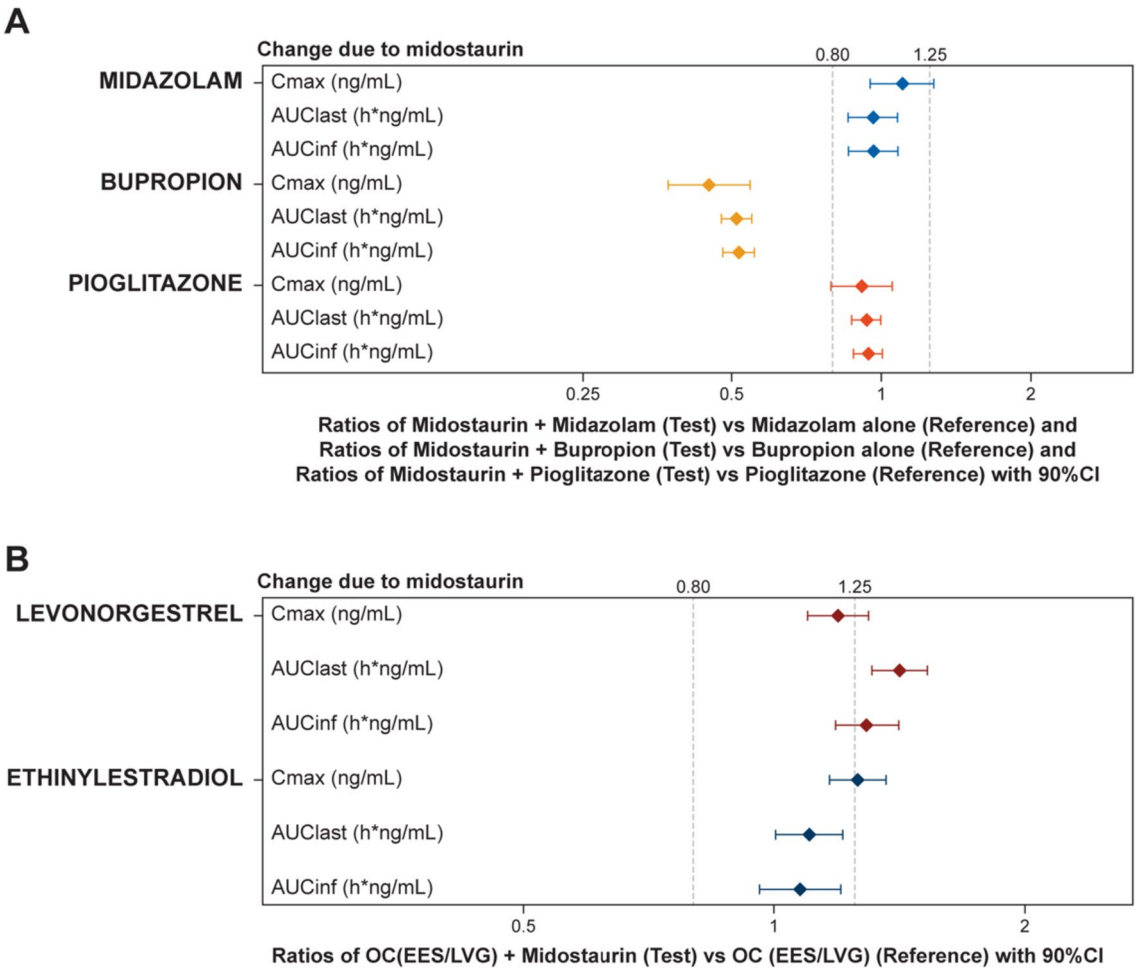

Fig. 2 PK parameters of **A** midazolam, bupropion, and pioglitazone in healthy male and female participants in the Study 1 with CYP substrates (Arm 1 and Arm 2) **B** levonorgestrel and ethinylestradiol in healthy females with no childbearing potential in the Study 2 with oral contraceptives. AUC_{inf}, area under the plasma concentration–time curve extrapolated to infinity, AUC_{last} area under the curve to the last quantifiable concentration point, C_{max} observed maximum plasma

Similarly, the $T_{1/2}$ of CGP52421 in Study 1 with CYP substrates could only be reliably estimated for two participants; $T_{1/2}$ estimates were 8.43 h and 8.67 h in Arm 1, and 44.3 h and 110 h in Arm 2. The $T_{1/2}$ of CGP62221 in Study 2 with oral contraceptives was 19.9 h. Summaries of PK parameters for the midostaurin and its metabolites are provided in Online Resource 7 and Online Resource 8.

Safety and tolerability

Overall, in both studies, midostaurin, the three CYP substrates (midazolam, bupropion, and pioglitazone), and oral contraceptives were well tolerated in the healthy participants. List of reported AEs from both the studies is shown in Table 4 and Online Resource 9.

In Arm 1 of Study 1 with CYP substrates, at least one AE was reported in all ($n=15$; 100%) participants, but the majority ($n=14$; 93.3%) of participants had mild AEs, and none were severe in intensity. There were no study discontinuations due to AEs.

In Arm 2 of Study 2 with CYP substrates, a total of 11 (61.1%) participants reported at least one AE of either mild ($n=9$; 50.0%) or moderate ($n=3$; 16.7%) intensity. None of the reported AEs were severe. Among the two participants who discontinued the study, one participant discontinued due to a mild AE (rash maculo-papular and lip swelling) that was considered related to midostaurin. The second participant discontinued the study due to an AE (elevated AST and CPK) that was not considered to be related to midostaurin. No clinically relevant changes were observed in laboratory evaluations, except for the previously mentioned elevations of AST and CPK in one participant.

In Study 2 with oral contraceptives, a total of 16 (80%) participants had at least one AE; of which the majority ($n=16$; 80%) had mild and few ($n=2$; 10%) had moderate intensity AEs. None had severe AEs. A total of 49 AEs

Table 2 Statistical analysis of the effect of midostaurin on PK of midazolam and bupropion (Study 1 with CYP substrates—Arm 1) and the effect of midostaurin on PK of pioglitazone (Study 1 with CYP substrates—Arm 2)

PK parameter (unit)	Treatment	Adjusted GMR	Treatment comparison			
			Comparison	GMR	90% CI	
					Lower	Upper
Midazolam (Arm 1), $n=15$, (PAS1)						
C_{max} (ng/mL)	Midazolam (reference)	12.6	Test vs reference	1.10	0.95	1.28
	Midazolam + midostaurin (Test)	13.9				
AUC_{last} (h*ng/mL)	Midazolam (reference)	46.7	Test vs reference	0.96	0.86	1.08
	Midazolam + midostaurin (Test)	45.0				
AUC_{inf} (h*ng/mL)	Midazolam (reference)	49.4	Test vs reference	0.97	0.86	1.09
	Midazolam + midostaurin (Test)	47.7				
Bupropion (Arm 1), $n=15$, (PAS1)						
C_{max} (ng/mL)	Bupropion (reference)	108	Test vs reference	0.45	0.37	0.54
	Midostaurin + bupropion (Test)	48.5				
AUC_{last} (h*ng/mL)	Bupropion (reference)	477	Test vs reference	0.51	0.48	0.55
	Midostaurin + bupropion (Test)	244				
AUC_{inf} (h*ng/mL)	Bupropion (reference)	502	Test vs reference	0.52	0.48	0.56
	Midostaurin + bupropion (test)	260				
Pioglitazone (Arm 2), $n=16$, (PAS2)						
C_{max} (ng/mL)	Pioglitazone (reference)	1010	Test vs reference	0.90	0.78	1.03
	Midostaurin + pioglitazone (Test)	913				
AUC_{last} (h*ng/mL)	Pioglitazone (reference)	11,200	Test vs reference	0.94	0.87	1.00
	Midostaurin + pioglitazone (Test)	10,500				
AUC_{inf} (h*ng/mL)	Pioglitazone (reference)	11,200	Test vs reference	0.94	0.88	1.01
	Midostaurin + pioglitazone (Test)	10,600				

AUC area under the curve, C_{max} observed maximum plasma (or serum or blood) concentration following administration (mass/volume), *CV%* coefficient of variation calculated as 100* SQRT(eMSE-1), n number of subjects with non-missing values, *PAS* pharmacokinetic analysis set, *SE* standard error

The log-transformed PK parameters were analyzed using an analysis of variance (ANOVA) model with a fixed effect for treatment and a random effect for subject

were reported of which the majority were mild, and 7 were of moderate intensity. Of the reported moderate intensity AEs, three were considered to be midostaurin related, one was oral contraceptive related, and three were not treatment related. The majority of AEs occurred during the multiple dosing period of midostaurin including the combined treatment period with oral contraceptive. The Investigator suspected that 26 of the 49 AEs were related to the midostaurin treatment. There were no clinically relevant changes seen in laboratory parameters, 12-lead ECGs, or vital signs values.

There were no SAEs or deaths reported in either of the studies.

PBPK model

The PBPK model using Simcyp® was applied to predict the potential impact of midostaurin at 100 mg twice daily dosing on midazolam or EES exposures. The predicted AUC ratio values of midazolam and EES, in the absence and presence of midostaurin 100 mg twice daily was 0.86 and 0.96, respectively. These findings indicate that the PK exposure of midazolam or EES was not affected by midostaurin at 100 mg twice daily. For LVG, there was an increase in mean C_{max} by 19% and total exposure (AUCs) by 29–42%, when midostaurin 50 mg twice daily at steady state was co-administered with oral contraceptive, as compared to when the oral contraceptive was administered alone. The observed slight increases in total exposures of EES (between 7 and 10%) and LVG (between 29 and 42%) with the effect from midostaurin 50 mg twice daily, suggests no-to-very weak DDI with EES and LVG. Since, the validated LVG PBPK model was not available, the extrapolation to midostaurin 100 mg twice daily on LVG was not conducted. However, the projected midazolam, which is a more sensitive substrate of CYP3A4 than LVG, showed a projected interaction AUC ratio of ~ 0.86 with midostaurin at 100 mg twice daily. Therefore, based on the PBPK modeling, there is no clinically significant impact of midostaurin at 50 or 100 mg twice

Table 3 Summary statistics of plasma PK parameters of EES and LVG components of monophasic oral contraceptives (Study 2 with oral contraceptives)

Statistics	C_{max} (ng/mL)	T_{max} (h)[a]	AUC_{last} (h*ng/mL)	AUC_{inf} (h*ng/mL)	$T_{1/2}$ (h)[a]	CL/F (L/h)	Vz/F (L)
Summary statistics of estrogen component, EES plasma PK parameters (PAS1)							
Oral contraceptive (EES/LVG) (day 1) $N=19$	0.0551 (0.0164)	1.50 (1.00; 4.00)	0.609 (0.227)	1.14 (0.234) *n = 4*	18.4 (11.5; 32.5) *n = 18*	27.1 (5.36) *n = 4*	840 (97.4) *n = 4*
Oral contraceptive (EES/LVG) + midostaurin (day 29) $N=19$	0.0687 (0.0180)	2.00 (1.00, 4.03)	0.679 (0.275)	1.06 (0.323) *n = 8*	15.4 (8.21; 31.1) *n = 18*	31.1 (10.4) *n = 8*	633 (153) *n = 8*
Summary statistics of progesterone component, LVG plasma PK parameters (PAS1)							
Oral contraceptive (EES/LVG) (day 1) $N=19$	3.51 (1.52)	1.50 (0.50; 2.88)	41.7 (19.7)	56.6 (17.0) *n = 13*	35.7 (19.6; 49.1) *n = 18*	2.90 (1.06) *n = 13*	126 (40.0) *n = 13*
Oral contraceptive (EES/LVG) + midostaurin (day 29) $N=19$	4.07 (1.30)	1.00 (1.00; 4.03)	57.6 (22.0)	66.6 (20.2) *n = 16*	31.2 (17.5; 75.7)	2.49 (0.879) *n = 16*	107 (47.1) *n = 16*

AUC area under the curve, *CL/F* clearance, C_{max} observed maximum plasma (or serum or blood) concentration following administration (mass/volume), *EES* ethinylestradiol, *LVG* levonorgestrel, *N* number of participants in respective treatment group, *n* number of subjects having respective non-missing PK parameter value in respective treatment group, *PAS* Pharmacokinetic analysis set, *PK* pharmacokinetic, $T_{1/2}$ elimination half-life, T_{max} time to reach peak or maximum concentration, *Vz/F* apparent volume of distribution

[a]Values are mean (SD), except T_{max} and $T_{1/2}$ are median (min;max)

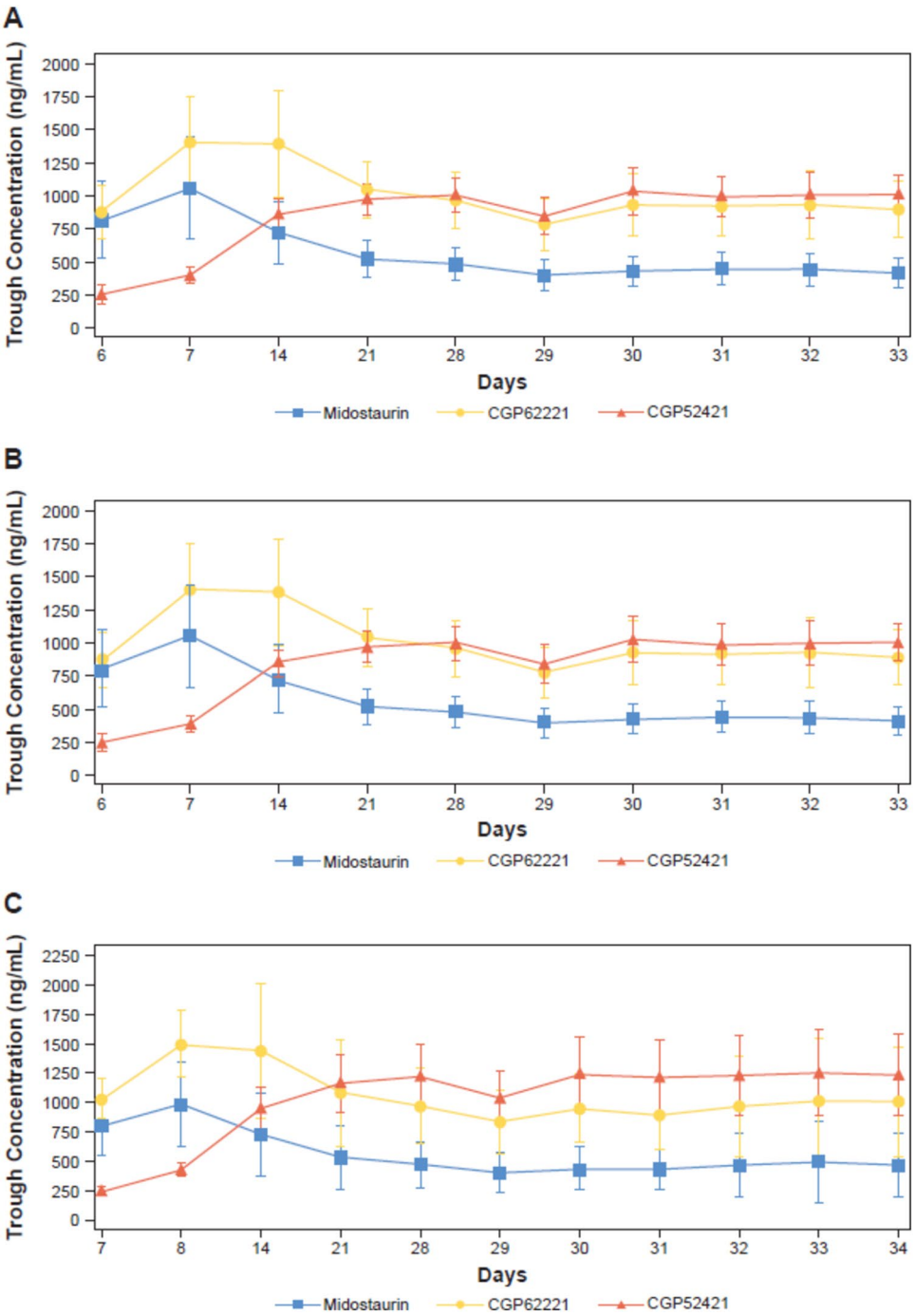

Fig. 3 Arithmetic mean (SD) midostaurin, CGP62221, and CGP52421 trough concentration–time profiles **A** in healthy male and female participants in Study 1 with CYP substrates—Arm 1 **B** in healthy male and female participants in Study 1 with CYP substrates—Arm 2 **C** in healthy females with no childbearing potential in Study 2 with oral contraceptives

daily on oral contraceptive exposure. This conclusion is supported by the slight changes in oral contraceptive exposure observed following midostaurin at 50 mg twice daily.

Novartis Safety Database (Argus) searches

Safety and pregnancies

This search strategy retrieved a total of 30 cases, of which only 8 relevant cases (involving mothers) were identified, where either pregnancy-related events or outcomes were reported. Of the eight cases who became pregnant while taking midostaurin, just one was using oral contraceptives (ingredients unspecified); however, information regarding DDI was not provided for this case.

Safety and oral contraceptives

The second search for concomitant use of oral contraceptives retrieved a total of 12 cases (all reports from clinical trials).

Table 4 Incidence of AEs (≥ 10%) by PTs

Study 1 with CYP substrates—Arm 1	Midazolam + bupropion	Midostaurin + midazolam + bupropion	Total	Mild grade	Moderate grade
	N = 15, *n* (%)	*N* = 15, *n* (%)	*N* = 15, *n* (%)	*n*	*n*
Somnolence	6 (40.0)	10 (66.7)	10 (66.7)	2	8
Nausea	0	5 (33.3)	5 (33.3)	2	3
Feeling abnormal	1 (6.7)	3 (20.0)	4 (26.7)	4	0
Headache	0	4 (26.7)	4 (26.7)	2	2
Abdominal discomfort	0	3 (20.0)	3 (20.0)	3	0
Fatigue	0	3 (20.0)	3 (20.0)	2	1
Abdominal pain	0	2 (13.3)	2 (13.3)	2	0
Abdominal pain upper	0	2 (13.3)	2 (13.3)	2	0
Back pain	1 (6.7)	1 (6.7)	2 (13.3)	1	1
Dizziness	1 (6.7)	1 (6.7)	2 (13.3)	2	0
Dry mouth	0	2 (13.3)	2 (13.3)	2	0
Taste disorder	1 (6.7)	1 (6.7)	2 (13.3)	2	0
Study 1 with CYP substrates—Arm 2	Pioglitazone	Midostaurin + pioglitazone	Total		
	N = 18, *n* (%)	*N* = 16, *n* (%)	*N* = 18, *n* (%)	*n*	*n*
Nasopharyngitis	0	5 (27.8)	5 (27.8)	5	0
Nausea	1 (5.6)	4 (22.2)	4 (22.2)	4	0
Headache	1 (5.6)	2 (11.1)	3 (16.7)	3	0
Study 2 with oral contraceptives	Oral contraceptive (EES/LVG)	Oral contraceptive (EES/LVG) + midostaurin	Total		
	N = 20, *n* (%)	*N* = 19, *n* (%)	*N* = 20, *n* (%)	*n*	*n*
Headache	0	5 (26.3)	5 (25.0)	4	1
Nausea	1 (5.0)	3 (15.8)	4 (20.0)	3	1
Diarrhea	1 (5.0)	2 (10.5)	3 (15.0)	3	0
Fatigue	0	3 (15.8)	3 (15.0)	3	0
Nasopharyngitis	0	3 (15.8)	3 (15.0)	1	2
Abdominal pain	0	2 (10.5)	2 (10.0)	2	0
Alopecia	0	2 (10.5)	2 (10.0)	2	0
Oropharyngeal pain	0	2 (10.5)	2 (10.0)	2	0

EES ethinylestradiol, *LVG* levonorgestrel, *n* number of subjects with at least 1 AE in the category, *OC* oral contraceptive, *PT* preferred term

A subject with multiple AEs is counted only once in the "Number of subjects with at least one AE" row

A subject with multiple AEs with the same PT is counted only once for that PT and treatment. PTs are sorted in descending frequency, as reported in the "Total" column

However, in none of these cases, event DDI was reported as an AE.

Discussion

Both studies provide highly relevant insights into the interaction potential of midostaurin with CYP substrates (midazolam, bupropion, and pioglitazone) and oral contraceptives (EES and LVG). To ensure safety of the healthy participants during administration of a dose of midostaurin 50 mg twice daily over a 28-day cycle, innovative study designs using a sentinel dosing approach were implemented, along with full confinement and safety measures. The stepwise dosing approach involved close monitoring of the participants for any safety concerns before proceeding to the next cohort with partial confinement.

In Study 1 with CYP substrates, we showed that in the presence of midostaurin 50 mg twice daily at steady state, peak exposure of midazolam was slightly increased by 10%, whereas total exposures (AUCs) of midazolam were almost unchanged, as they decreased only by 3–4%. Regarding bupropion, there was a 55% decrease in mean peak plasma concentrations and a 48–49% decrease in total exposures.

For pioglitazone, there was a 10% decrease in mean peak plasma concentrations and a 6% decrease in total exposures. These findings indicate that the net effect of midostaurin is neither an inhibitor nor an inducer of CYP3A4 and CYP2C8, while it is a weak inducer of CYP2B6.

In Study 2 with oral contraceptives, midostaurin showed a minor inhibitory effect on the metabolism of EES and a mild inhibitory effect on LVG. In the presence of midostaurin at steady state, the mean peak plasma concentrations of EES increased by 26% and total exposure increased by 7–10%, compared to when the oral contraceptive was administered alone. Similarly, in the presence of midostaurin at steady state, mean peak plasma concentrations of LVG increased by 19% and total exposure increased by 29–42%, compared to oral contraceptive administration alone. Thus, when midostaurin is used at a dose of 50 mg twice daily concomitantly with oral contraceptives, no clinically relevant PK-based drug interaction is observed. Considering there was no decrease in EES and LVG levels by midostaurin, reliable contraception can thereby be maintained. Therefore, the present study confirms that the observed slight increases in PK exposures of EES and LVG do not impact the reliability of contraception.

Steady-state trough plasma concentrations of midostaurin and its metabolites CGP62221 and CGP52421 were achieved approximately after two to three weeks of twice daily dosing with 50 mg midostaurin. This ensured steady-state conditions during the administrations of CYP substrate drugs or oral contraceptive dosing in Period 2 of Study 1 (both study Arms) and in Study 2. The median apparent $T_{1/2}$ for midostaurin was comparable between the two arms of Study 1. The median $T_{1/2}$ for CGP62221 was 38.6 h, 49.9 h in Arms 1 and 2 of Study 1 and 19.9 h, in Study 2, respectively. Midostaurin peak and total steady-state exposures were similar between the two studies. The midostaurin peak concentration and total steady state exposures ranged from 888 to 1040 ng/mL, and 6350–7680 h*ng/mL, respectively. Similarly, peak, and total steady-state exposures of CGP62221 ranged from 978 to 1110 ng/mL and 10,700–12,100 h*ng/mL, respectively. The $T_{1/2}$ of midostaurin and CGP62221 were consistent with previously reported results unlike the $T_{1/2}$ of CGP52421 [1, 2, 4]. The apparent $T_{1/2}$ determined for CGP52421 in the present study with the rich PK data collection is in agreement with the time to reach steady state in a clinical setting of repeated dosing with the marketed formulation.

In accordance with the EMA [10] and FDA [14] guidelines on the investigation of drug interactions, it is concluded that twice daily midostaurin 50 mg administered under steady-state conditions has no clinical significant effect on the metabolism of midazolam (a CYP3A substrate) or pioglitazone (a CYP2C8 substrate), but is a weak inducer of CYP2B6, based on its effect on bupropion (CYP2B6 substrate). Thus, as reflected in the updated labels, dose adjustments for co-administered CYP2B6 substrates may be necessary [1] and medicinal products with a narrow therapeutic range that are substrates of CYP2B6 (e.g., bupropion or efavirenz) should be used with caution when administered concomitantly with midostaurin and may need dose adjustment to maintain optimal exposure [2].

Notably, only slight increases were observed from midostaurin 50 mg twice daily in total exposures of EES and LVG. In line with the EMA [10] and FDA [14] guidelines, it is concluded that midostaurin 50 mg twice daily administered under steady-state conditions has a minor inhibitory effect on the metabolism of EES and a mild inhibitory effect on LVG.

Furthermore, PBPK modeling extrapolated the results from Study 2 to a twice daily dosage of 100 mg midostaurin. This modeling aimed to ensure the reliability of oral contraceptives for patients with advSM on the recommended dose of midostaurin 100 mg twice daily. The results of the PBPK modeling showed that concomitant administration of oral contraception together with midostaurin at doses of either 50 mg or 100 mg twice daily is not associated with a clinically relevant PK-based drug-drug interaction. Therefore, the present study results confirm that midostaurin (when dosed either at 50 mg or 100 mg twice daily) is used concomitantly with hormonal contraceptives; no clinically relevant PK-based drug interaction is observed. Based on the analysis of the low number of pregnancy cases reported in patients with AML (on midostaurin 50 mg bid) and AdvSM (on midostaurin 100 mg bid), no trend could be detected due to a potentially decreased reliability of oral contraception. As reflected in the label [1], it is not anticipated that oral contraceptive reliability will be compromised by co-administration of midostaurin. However [2], the effect during the first week, when midostaurin trough concentrations are highest, is unknown (See the midostaurin labels for more information).

Overall, midostaurin and the CYP drug substrates (midazolam, bupropion, and pioglitazone) and oral contraceptives demonstrated acceptable safety and tolerability profiles when administered alone or in combination. No safety concerns associated with combination treatment were reported.

Consequently, the label of midostaurin (Rydapt) and the summary of product characteristics [1] were adjusted to include these findings and the corresponding interaction liabilities of these medications were removed or adapted as appropriate.

Conclusion

Using a sentinel dosing approach to ensure participants' safety, the effects of midostaurin at steady state following 25-days at a dose of 50 mg twice daily were evaluated on

CYP drug substrates, midazolam (CYP3A4), bupropion (CYP2B6), and pioglitazone (CYP2C8) in Study 1; and following 24 days was evaluated on monophasic oral contraceptives (containing EES and LVG) in Study 2. Overall, midostaurin neither inhibits nor induces CYP3A4 and CYP2C8, however, weakly induces CYP2B6. Therefore midostaurin has no clinically relevant interactions expected on CYP3A and CYP2C8 substrate drugs. Dose adjustments might be required for medicinal products with a narrow therapeutic range that are substrates of CYP2B6 (e.g., bupropion or efavirenz). Study 2 showed that midostaurin has a minor inhibitory effect on the metabolism of EES and a mild inhibitory effect on LVG. Extrapolation of the results from Study 2 with oral contraceptives to 100 mg twice daily of midostaurin using PBPK modeling also showed similar results. Therefore, when midostaurin dosed either at 50 mg or 100 mg twice daily at steady state is used concomitantly with hormonal contraceptives, there is no clinically relevant PK-based drug interaction. Midostaurin and the three CYP substrates and oral contraceptive were well tolerated, and the AEs reported were consistent with the known safety profile of the drug.

The corresponding interaction liabilities were adjusted accordingly in the labels and summary of product characteristics of midostaurin as appropriate.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00280-023-04635-3.

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Author contributions RS, HG, GR, AT, OC, GKS, AB, and HDM performed conception and design, data review and interpretation, drafting the manuscript, critical revision of the manuscript for important intellectual content, and final approval of the manuscript.

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Availability of data and materials Novartis is committed to sharing with qualified external researchers, access to patient/participant-level data and supporting clinical documents from eligible studies. These requests are reviewed and approved by an independent review panel on the basis of scientific merit. All data provided are anonymized to respect the privacy of patients/participants who have participated in the trial in line with applicable laws and regulations.

Declarations

Conflict of interest R Sechaud, G Rahmanzadeh, and H Menssen are employees of Novartis Pharma AG, Switzerland. H Gu, A Taylor, O Chiparus, are employees of Novartis Pharmaceuticals Corporation, USA. GK Sharma is an employee of Novartis Healthcare Pvt. Ltd., India. A Breitschaft is an employee of Parexel International GmbH, Germany.

Ethical approval and informed consent Both the studies were performed in accordance with the ethical principles, which have their origin in the Declaration of Helsinki and are consistent with Good Clinical Practice and applicable regulatory requirements. All participants of the study provided written informed consent according to international standards. Both studies were conducted at the Early Phase Clinical Unit of PAREXEL International GmbH in Berlin, Germany. The study protocols were reviewed and approved by the State Office of Health and Social Affairs Ethics Committee of Berlin (Landesamt für Gesundheitund Soziales Ethik-Kommission des Landes Berlin) for PAREXEL International GmbH. Study 1 with CYP substrates and Study 2 with oral contraceptives were registered under EudraCT number: 2018-002786-19 and EudraCT number: 2018-002867-25, respectively, and both obtained a favorable opinion from the IEC. The study participants were informed about the study procedures, risks, and benefits of their participation. Informed consent was documented by the investigator.

References

1. EMA (2017) Rydapt. https://www.ema.europa.eu/en/medicines/human/EPAR/rydapt. Accessed 25 Apr 2023
2. FDA (2021) RYDAPT® (midostaurin) capsules, for oral use Initial US. Approval: 2017. https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/207997s008lbledt.pdf. Accessed 09 Sep 2023
3. Gu H, Dutreix C, Rebello S, Ouatas T, Wang L, Chun DY, Einolf HJ, He H (2018) Simultaneous physiologically based pharmacokinetic (PBPK) modeling of parent and active metabolites to investigate complex CYP3A4 drug-drug interaction potential: a case example of midostaurin. Drug Metab Dispos 46(2):109–121. https://doi.org/10.1124/dmd.117.078006
4. He H, Tran P, Gu H, Tedesco V, Zhang J, Lin W, Gatlik E, Klein K, Heimbach T (2017) Midostaurin, a novel protein kinase inhibitor for the treatment of acute myelogenous leukemia: insights from human absorption, metabolism, and excretion studies of a BDDCS II drug. Drug Metab Dispos 45(5):540–555. https://doi.org/10.1124/dmd.116.072744
5. Nordt SP, Clark RF (1997) Midazolam: a review of therapeutic uses and toxicity. J Emerg Med 15(3):357–365. https://doi.org/10.1016/S0736-4679(97)00022-X
6. FDA (2017) WELLBUTRIN® (bupropion hydrochloride) tablets, for oral use Initial US. Approval: 1985. https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/018644s052lbl.pdf
7. FDA (2011) ACTOS (pioglitazone hydrochloride) tablets for oral use Initial US. Approval: 1999 https://www.accessdata.fda.gov/drugsatfda_docs/label/2011/021073s043s044lbl.pdf. Accessed 5 May 2023
8. FDA (2020) In vitro drug interaction studies—cytochrome P450 enzyme- and transporter-mediated drug interactions guidance for industry. https://www.fda.gov/media/134582/download. Accessed 18 Jun 2023
9. EMA (2012) EMA Guideline on the investigation of drug interactions. https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-investigation-drug-interactions-revision-1_en.pdf. Accessed 18 Jun 2023
10. Gibbons JA, de Vries M, Krauwinkel W, Ohtsu Y, Noukens J, van der Walt JS, Mol R, Mordenti J, Ouatas T (2015) Pharmacokinetic drug interaction studies with enzalutamide. Clin Pharmacokinet 54(10):1057–1069. https://doi.org/10.1007/s40262-015-0283-1
11. Bosilkovska M, Samer CF, Déglon J, Rebsamen M, Staub C, Dayer P, Walder B, Desmeules JA, Daali Y (2014) Geneva cocktail for cytochrome P450 and P-glycoprotein activity assessment

using dried blood spots. Clin Pharmacol Ther 96(3):349–359. https://doi.org/10.1038/clpt.2014.83
12. Dutreix C, Munarini F, Lorenzo S, Roesel J, Wang Y (2013) Investigation into CYP3A4-mediated drug–drug interactions on midostaurin in healthy volunteers. Cancer Chemother Pharmacol 72(6):1223–1234. https://doi.org/10.1007/s00280-013-2287-6
13. FDA (2020) Clinical drug interaction studies—cytochrome P450 enzyme- and transporter-mediated drug interactions guidance for industry. https://www.fda.gov/media/134581/download. Accessed 23 Jun 2023
14. Sechaud R, Sinclair K, Grosch K, Ouatas T, Pathak D (2022) Evaluation of drug-drug interactions between midostaurin and strong CYP3A4 inhibitors in patients with FLT-3-mutated acute myeloid leukemia (AML). Cancer Chemother Pharmacol 90(1):19–27. https://doi.org/10.1007/s00280-022-04448-w
15. Gu H, Sechaud R, Hanna I, Pelis R, Einolf H (manuscript in preparation) Physiologically based pharmacokinetic modeling of midostaurin and metabolites at steady state to bridge drug interaction scenarios in lieu of clinical trials