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ORIGINAL ARTICLE

Clinical evaluation of the potential drug–drug interactions of savolitinib: Interaction with rifampicin, itraconazole, famotidine or midazolam

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Aims: We investigated savolitinib pharmacokinetics (PK) when administered alone or in combination with rifampicin, itraconazole or famotidine, and investigated midazolam PK when administered with or without savolitinib in healthy males.

Methods: Savolitinib PK was evaluated before/after: rifampicin (600 mg once daily [QD] for 5 days); itraconazole (200 mg QD for 5 days); a single dose of famotidine (40 mg QD) 2 hours before savolitinib. Midazolam PK was evaluated before/after midazolam (1 mg QD) with or without savolitinib (600 mg QD). Each study enrolled 20, 16, 16 and 14 volunteers, respectively. Plasma samples were collected to determine the effect on PK.

Results: The geometric mean ratios (GMR, %) (90% confidence intervals [CIs]) for savolitinib alone and in combination for C_{max}, AUC respectively, were 45.4 (41.4–49.9), 38.5 (34.2–43.3) in the rifampicin study ($n = 18$); 105.2 (87.7–126.3), 108.4 (96.3–122.1) in the itraconazole study ($n = 16$); and 78.8 (67.7–91.7), 87.4 (81.2–94.2) in the famotidine study ($n = 16$). The GMRs (90% CIs) for midazolam

The authors confirm that the Principal Investigator for the itraconazole study reported in this paper is David Han, MD, and for the rifampicin, midazolam and famotidine studies is Ronald Goldwater, MD, and they had direct clinical responsibility for volunteers in the respective studies.

alone and in combination with savolitinib for C_{max}, AUC respectively, were 84.1 (70.0–101.0), 96.7 (92.4–101.1) ($n = 14$). Savolitinib alone or in combination was well tolerated.

Conclusions: Co-dosing of rifampicin significantly reduced exposure to savolitinib *vs* savolitinib alone; co-dosing of itraconazole or midazolam with savolitinib had no clinically significant effect on savolitinib or midazolam PK, respectively. Co-dosing of famotidine with savolitinib reduced exposure to savolitinib, although this was not considered clinically meaningful. No new savolitinib-related safety findings were observed.

KEYWORDS
cytochrome P450, drug interactions, therapeutics

1 | INTRODUCTION

The **MET** receptor is an essential transmembrane receptor for embryonic development and wound healing, and is normally activated through interaction with its specific ligand, hepatocyte growth factor (**HGF**). The MET pathway is frequently dysregulated in human cancer; in several clinical studies, aberrant activation of MET signalling is associated with tumourigenesis, poor clinical outcomes, rapid disease progression and short survival in human cancers.[1,2] **Savolitinib** is an oral, potent and highly selective MET tyrosine kinase inhibitor (TKI), currently demonstrating preliminary clinical activity in advanced solid tumours.[3–6]

Single-dose savolitinib is rapidly absorbed with a relatively short time to peak (t_{max}) (around 2–4 hours[h]); the maximum plasma concentration (C_{max}) and the area under the plasma concentration curve (AUC) appear to show proportionality across the dose ranges investigated[5]; at savolitinib 600 mg once daily (QD), C_{max} was 2414.8 ng/mL, AUC was 17 053.9 h.ng/mL, and there was no apparent drug accumulation.[6] The apparent terminal half-life ($t_{½λz}$) is short (ranges from 3.8–6.8 h; dose ranges from 100–1000 mg QD and 300–500 mg twice daily [BD]) and, as a result, there is no accumulation of savolitinib after QD or BD dosing.[6] In previous studies, the mean plasma exposure of the pharmacologically active metabolite, M2 (N-desmethyl savolitinib), and a non-pharmacologically active metabolite, M3 (hydroxy savolitinib), was approximately 21–38% and 10–13% of the exposure of savolitinib, respectively (based on AUC from time 0–48 h after a single dose of savolitinib[7,8]). The recommended Phase 2 dose of savolitinib monotherapy was established as 600 mg QD.

Based on *in vitro* data, savolitinib metabolism appears to be mediated by multiple cytochrome P450 (CYP) enzymes, including **CYP3A4** and **CYP1A2** and non-CYP enzymes, such as uridine diphosphoglucuronosyltransferase (**UGT**; UGT1A4 and UGT2B15) and aldehyde oxidase (**AO**) (data on file) (Appendix Figure A1). Although the exact contribution of each of these enzymes to the elimination is not known, as CYP3A4 is one of the routes of metabolism for savolitinib and a major enzyme involved in metabolism of multiple drugs, understanding the impact on the exposure to savolitinib and its metabolites is specifically important for potential combination treatments with other anticancer agents that may be inhibitors or inducers of CYP3A. As the contribution of CYP1A2 was unclear, and the preliminary human population PK analysis suggested that the exposure of savolitinib was not impacted by smoking status, the impact of CYP1A2 has not been evaluated at this time.

Savolitinib and M2 show good permeability in caco-2 cells and are not efflux transport substrates; however, in Madin-Darby Canine Kidney (MDCK) cells with the MDR1 gene, savolitinib is a P-glycoprotein (P-gp) substrate. Nevertheless, it should be noted that due to high intrinsic permeability and linear PK over the 100–1000 mg dose range, clinically relevant DDIs due to P-gp inhibition are unlikely. *In vitro* metabolism studies indicated that M2 formation from savolitinib is largely driven by CYP1A2 and CYP2C19, while M3 is likely driven by AO. Further M2 metabolism occurs through glucuronidation and is predominately driven by UGT1A4 and UGT2B15 isoforms, although some metabolism is also

What is already known about this subject

- Savolitinib is a potent, oral MET inhibitor whose solubility is pH dependent.
- *In vitro* data indicates that savolitinib is metabolised by CYP3A4 and may be an inhibitor of CYP3A4 and inducer of CYP3A via pregnane X receptor (PXR).

What this study adds

- Savolitinib exposure is not affected by CYP3A4 inhibitors and gastric pH modifiers; however, its exposure is affected by strong CYP3A inducers.
- Savolitinib does not affect the exposure of CYP3A4 substrates.

driven by further CYP oxidation [data on file]. In accordance with the US Food and Drug Administration (FDA) and European Medicines Agency (EMA) guidance, we conducted four drug–drug interaction (DDI) studies in healthy, male volunteers to determine whether exposure to savolitinib is potentially affected by concomitant medication or if savolitinib affects exposure to concomitant medication.[9,10]

Co-administration of compounds that induce or inhibit enzymes and/or transporters involved in elimination of savolitinib are hypothesised to decrease or increase systemic exposure to savolitinib, respectively.[9] Therefore, we sought to quantify the effect of the potent CYP3A4 enzyme and transporter inducer, **rifampicin**[11] and the CYP3A4 and P-gp inhibitor, **itraconazole**,[12] on savolitinib pharmacokinetics (PK). Gastric pH increases produced by concomitant therapies, such as **H2 receptor** antagonists (H2RA), may decrease the solubility or gastrointestinal dissolution of savolitinib, thus altering the rate and/or extent of absorption.[13] Therefore, we examined the effect of famotidine, an H2RA that raises gastric pH after a single dose, on savolitinib PK; **famotidine** is considered to be representative of various gastric acid modifiers and was selected for its potency.[14]

A recent clinical study with savolitinib showed that a high fat meal increased AUC by approximately 18%, while C_{max} remained unchanged.[15] Given that the incidence of gastrointestinal adverse events (AEs) was higher in the fasted state than in the fed state, when savolitinib was administered with food,[15] savolitinib was administered within 15 minutes after a meal in all four DDI studies.

In clinical practice, savolitinib may be co-administered with CYP3A substrates; *in vitro* data suggest savolitinib and/or its metabolites could inhibit CYP3A4 and has low potential to induce CYP3A (see Supporting Information). To understand the potential effect of savolitinib on the CYP3A metabolic pathway, we evaluated the impact of savolitinib on the **midazolam** PK as an index drug representative for other CYP3A substrates.[16]

We report results from four Phase 1 DDI studies, investigating the effect of savolitinib with either rifampicin (NCT04118842), itraconazole (NCT04121910), famotidine (NCT04179071) or midazolam (NCT04187456).

2 | METHODS

2.1 | Participants

Key inclusion criteria for all studies included: healthy adult male volunteers, aged 18–65 years, and 50–100 kg (inclusive), with non-Japanese ethnicity. Full inclusion and exclusion criteria are shown in the Supporting Information. All study centres were in the US, with all studies based in Baltimore (Parexel Early Phase Clinical Unit, Baltimore, MD), other than the itraconazole study, which was based in California (Parexel Early Phase Clinical Unit, Los Angeles, CA). The studies were conducted in accordance with ethical principles that had their origin in the Declaration of Helsinki and were consistent with International Conference on Harmonization–Good Clinical Practice guidance; protocols were reviewed and approved by an Institutional Ethics Committee and Institutional Review Board. Informed consent was obtained from all volunteers.

2.2 | Study designs

The four DDI studies were open-label, multi-part studies. Study designs are shown in Figure 1, with full details and dosing information in the Supporting Information.

The rifampicin and itraconazole studies each involved three treatment periods (TP), whilst the famotidine and midazolam studies each involved two.

In the rifampicin study, volunteers received: savolitinib 600 mg alone on Day 1 followed by a 14-day washout period (TP1), rifampicin 600 mg QD on Days 15–19 (TP2), and savolitinib 600 mg alone on Day 20 plus rifampicin 600 mg QD on Days 20–22 (TP3). Volunteers in the itraconazole study received: savolitinib 200 mg alone on Day 1 followed by a 14-day washout period (TP1), itraconazole 200 mg BD on Day 15 and QD on Days 16 and 17 (TP2), and savolitinib 200 mg alone on Day 18 plus itraconazole 200 mg QD on Days 18 and 19 (TP3).

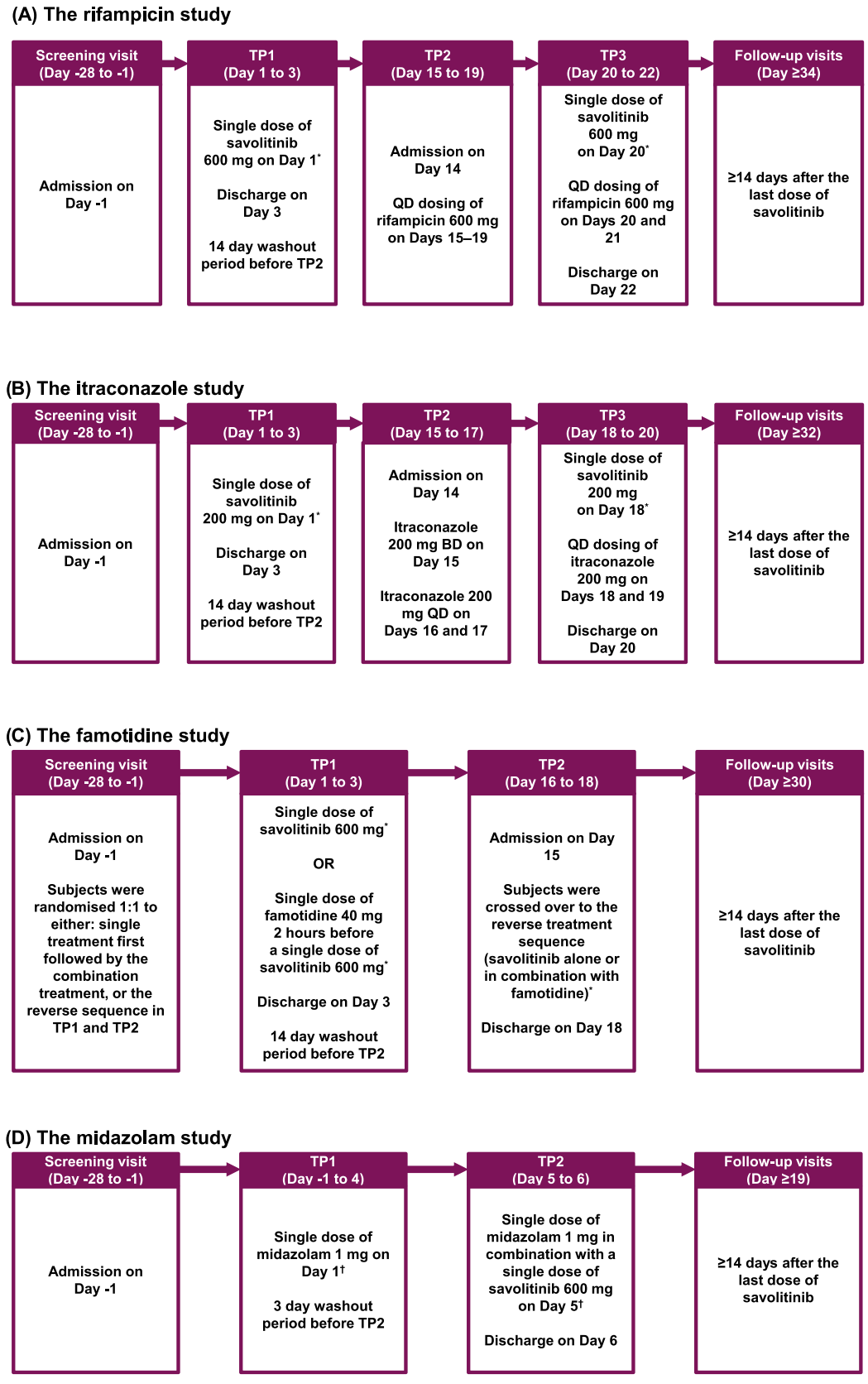
In Part A of the famotidine randomised, crossover study, half of the volunteers received savolitinib 600 mg alone and the other half received famotidine 40 mg plus savolitinib 600 mg 2 h later, followed by a 14-day washout period (TP1); volunteers then received the reverse treatment sequence (TP2). Part B of the study was to be conducted in a new group of healthy, non-Japanese male volunteers, if the results in Part A indicated an interaction between savolitinib and famotidine (defined as a mean decrease of 30% in savolitinib C_{max} or AUC after famotidine pre-treatment). Volunteers in the midazolam study received midazolam 1 mg alone on Day 1 followed by a 3-day washout period (TP1), and midazolam 1 mg plus savolitinib 600 mg on Day 5 (TP2).

In the rifampicin, itraconazole and famotidine studies, plasma PK samples for savolitinib, M2 and M3 were collected at pre-dose and at 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 12, 18, 24, 36 and 48 h after savolitinib administration; midazolam plasma PK samples were collected at pre-dose and at 0.25, 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 3, 4, 6, 8, 12, 16, and 24 h after midazolam administration.

2.3 | Objectives

The primary objective was to assess the effect of rifampicin, itraconazole and famotidine on savolitinib PK, and the effect of savolitinib on midazolam exposure (AUC and C_{max}).

The secondary objective was to assess the safety and tolerability of savolitinib alone and in combination with rifampicin, itraconazole and famotidine, and midazolam alone and in combination with savolitinib. In all studies, safety was assessed by adverse events (AEs), physical examination, vital signs, resting 12-lead electrocardiogram



*Plasma PK samples for savolitinib, M2 and M3 were collected at pre-dose and at 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 12, 18, 24, 36 and 48 h after savolitinib administration
†Plasma PK samples for midazolam were collected at pre-dose and at 0.25, 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 3, 4, 6, 8, 12, 16, and 24 h after midazolam administration
BD, twice daily; QD, once daily; TP, treatment period

FIGURE 1 Study designs of (A) the rifampicin study ($N = 20$), (B) the itraconazole study ($N = 16$), (C) the famotidine study ($N = 16$), (D) the midazolam study ($N = 14$)

(ECG) and laboratory parameters. AEs were collected until last follow-up and classified according to Medical Dictionary for Regulatory Activities (MedDRA) version 22.1.

With the exception of the midazolam study, further secondary objectives were to assess the effect of each drug on the PK of savolitinib metabolites, M2 and M3, and to describe the additional PK parameters and profiles for savolitinib, M2 and M3 when savolitinib is administered alone and in combination with each drug. Another secondary objective in the midazolam study was to describe midazolam PK in the presence and absence of savolitinib; to evaluate the PK of savolitinib, M2 and M3 when administered in combination with midazolam was included as an exploratory endpoint.

2.4 | Statistical methods

Proposed sample sizes of all studies were selected to give adequate information on the effect of the study drug (rifampicin, itraconazole and famotidine) on the exposure of savolitinib and the effect of savolitinib on the exposure of midazolam, while exposing as few volunteers as possible to study procedures and drugs.

In the rifampicin, itraconazole and famotidine studies, the estimated geometric mean ratio (GMR) and the associated 90% confidence interval (CI) between the combination of savolitinib with study drug and savolitinib alone for AUC, C_{max} (primary) and AUC from time zero to time of last quantifiable concentration ($AUC_{[0\text{-}t]}$) (secondary) was determined. If the true intra-subject coefficient of variation (CV) was 30%, 14 evaluable volunteers were expected to give a relative precision of 1.56 (ratio between the upper and lower limits of the 90% CI) with 80% probability. This would provide sufficient precision to interpret the clinical relevance of potential DDIs and correspond to a 90% CI of 0.80–1.25 if the observed ratio was 1.00; if the relative precision was 1.6, it would correspond to a 90% CI of 0.79–1.26. To account for potential discontinuations, 16 volunteers were to be enrolled in each of these studies. In the midazolam study, assuming the within-subject CV of 18% for AUC, 12 evaluable volunteers were expected to give >80% power to show that the 90% CI for a true GMR of 1.00 would be between 0.80–1.25. Although C_{max} is slightly more variable (CV of 23%), 12 volunteers were expected to provide sufficient precision for the C_{max} ratio as well (90% CI between 0.70 and 1.43). To account for potential discontinuations, 14 volunteers were to be included in this study.

The safety analysis set included volunteers who received at least one dose of any study drug, or midazolam in the midazolam study, and for whom any post-dose safety data were available; this set was used for the presentation of demographic and disposition data, and all safety analyses.

The PK analysis set for each study included volunteers who received a savolitinib dose, had at least one quantifiable post-dose plasma concentration and had no important protocol deviations or events that impacted PK.

To assess the effect of rifampicin, itraconazole or famotidine on savolitinib PK and of savolitinib on midazolam PK, the GMRs and 90% CIs of the drug dosed in combination compared to alone for the PK parameters C_{max}, AUC and $AUC_{(0\text{-}t)}$ were determined for savolitinib, M2, M3 and midazolam, as appropriate for each study. An interaction between savolitinib and famotidine was considered to be potentially clinically meaningful if there was a mean decrease of >30% in the estimated GMRs of savolitinib C_{max} or AUC after pre-treatment with famotidine.

2.5 | Bioanalysis

In all studies, PK sample analysis was performed by Covance Laboratory in the US (Indianapolis, IN). Drug concentrations were determined by validated analytical methods using high-performance liquid chromatography and tandem mass spectrometry (HPLC–MS/MS).

Savolitinib, M2 and M3 concentrations were measured simultaneously in human plasma with sodium heparin as an anticoagulant. The linear range established was 1–1000 ng/mL with 100-fold dilution for each analyte. The precision and accuracy for the quality control samples in each study and the plasma concentrations of itraconazole and midazolam are reported in the Supporting Information. Plasma concentrations of rifampicin and famotidine were not measured.

2.6 | PK analysis

The plasma concentration–time data for savolitinib, M2, M3 and midazolam were analysed separately for all treatments, as appropriate for each study. Actual elapsed PK sample times were used to determine the PK parameters AUC, C_{max}, $AUC_{(0\text{-}t)}$, t_{max} and half-life associated with terminal slope (λz) of a semi-logarithmic concentration–time curve ($t_{½}\lambda z$) for savolitinib, M2, M3 and midazolam. Apparent total body clearance of drug from plasma after extravascular administration (CL/F) and apparent volume of distribution during the terminal phase after extravascular administration (Vz/F) were measured for savolitinib and midazolam, and metabolite-to-parent ratios of C_{max}, AUC and $AUC_{(0\text{-}t)}$ were measured for M2 and M3. All PK parameters were determined using non-compartmental methods with Phoenix® WinNonlin® Version 8.1; descriptive statistics and inferential statistical comparisons of treatments were performed using SAS® Version 9.4.

2.7 | Nomenclature of targets and ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, and are permanently archived in the Concise Guide to PHARMACOLOGY 2019/20.[17,18]

TABLE 1 Volunteer demographics by treatment (pharmacokinetic analysis set)

	Rifampicin study ($N = 20$)	Itraconazole study ($N = 16$)	Famotidine study ($N = 16$)	Midazolam study ($N = 14$)
Age (years), median (range)	39.5 (21–58)	40.5 (25–63)	36.5 (23–55)	34.5 (18–58)
Sex, *n* (%)				
Male	20 (100)	16 (100)	16 (100)	14 (100)
Race, *n* (%)				
White	5 (25)	12 (75)	6 (38)	4 (29)
Black or African American	12 (60)	4 (25)	9 (56)	9 (64)
Asian	2 (10)	0	1 (6)	0
American Indian or Alaska native	1 (5)	0	0	1 (7)
Ethnicity, *n* (%)				
Hispanic or Latino	4 (20)	3 (19)	2 (13)	3 (21)
Not Hispanic or Latino	16 (80)	12 (75)	14 (88)	11 (79)
Unknown	0	1 (6)	0	0
Height (cm), mean ± SD	179 ± 8	177 ± 8	177 ± 7	174 ± 11
Weight (kg), mean ± SD	83 ± 10	80 ± 10	78 ± 9	79 ± 12
Body mass index (kg/m^2), mean ±SD	26 ± 2	25 ± 3	25 ± 3	26 ± 3

Data presented as *n* (%), median (range) or mean ± SD.
n, number of datapoints included in the summary statistics; *N*, number of volunteers in the pharmacokinetic analysis set; SD, standard deviation; TP, treatment period.
Rifampicin study: TP1 (Days 1–14): savolitinib 600 mg once daily on Day 1; TP2 (Days 15–19): rifampicin 600 mg once daily on Days 15–19; TP3 (Days 20–22): savolitinib 600 mg once daily on Day 20 and rifampicin 600 mg once daily on Days 20 and 21; follow-up to Day 34.
Itraconazole study: TP1 (Days 1–14): savolitinib 200 mg once daily on Day 1; TP2 (Days 15–17): itraconazole 200 mg twice daily on Day 15 and itraconazole 200 mg once daily on Days 16 and 17; TP3 (Days 18–20): savolitinib 200 mg once daily on Day 18 and itraconazole 200 mg once daily on Days 18 and 19; follow-up to Day 32.
Famotidine study: on Day −1, volunteers were randomised 1:1 to either one of the two treatment sequences: single treatment (single oral dose of 600 mg savolitinib on Day 1) first followed by the combination treatment (single oral doses of 40 mg famotidine + 600 mg savolitinib on Day 16), or the reverse sequence, in TP1 and TP2; follow-up to Day 30.
Midazolam study: TP1 (Days −1–4): midazolam 1 mg once daily on Day 1; TP2 (Days 5–6): midazolam 1 mg once daily and savolitinib 600 mg once daily on Day 5; follow-up to Day 19.

3 | RESULTS

3.1 | Participants

Overall, 80% (16/20), 94% (15/16), 100% (16/16) and 93% (13/14) of volunteers completed all TPs, including follow-up, in the rifampicin, itraconazole, famotidine and midazolam studies, respectively. Volunteers across all studies were male, with median ages ranging from 34.5 to 40.5 years and mean BMIs between 25.2 and 25.9 kg/m.^{2} With the exception of the itraconazole study, most volunteers were black or African American, representing 56–64% of the study populations (25% in the itraconazole study); see volunteer demographics in Table 1.

3.2 | Pharmacokinetics

The PK parameters in all studies are summarised in Tables 2 and 3; PK parameters for M2 and M3 are listed in Appendix Tables A1 and A2.

3.3 | Rifampicin study

Two volunteers were excluded from the rifampicin PK analysis set for important protocol deviations; of the 18 volunteers included, two had available data for TP1 only due to early withdrawal from the study. One of these volunteers discontinued due to an AE of hypersensitivity, and the other was unable to complete the study for personal reasons. Savolitinib plasma concentrations were lower when savolitinib was dosed in combination with rifampicin compared with when dosed alone (Figure 2A), with corresponding reductions in exposure (Table 3). Exposure to savolitinib was significantly reduced, by 55% and 61% for C_{max} and AUC, respectively, when savolitinib was dosed in combination with rifampicin compared with when dosed alone (90% CIs for the GMRs did not include 100%). The GMRs (% [90% CIs]) for C_{max}, AUC and $AUC_{(0\text{-}t)}$ were 45.4 (41.4–49.9), 38.5 (34.2–43.3) and 37.8 (34.8–41.0), respectively (Table 3). Compared with savolitinib, similar changes in C_{max} and AUC (37% [55.3–71.4] and 49% [43.5–58.9] reduction, respectively) were seen for M2 across the TPs (Appendix Table A3); for M3, C_{max} increased by 40% (124.9–156.8) and $AUC_{(0\text{-}t)}$ decreased by 10%

TABLE 2 Descriptive statistics of savolitinib or midazolam pharmacokinetic parameters by treatment (pharmacokinetic analysis set)

	Rifampicin study		Itraconazole study		Famotidine study		Midazolam study	
	Savolitinib (*N* = 18)	Savolitinib + rifampicin (*N* = 16)	Savolitinib (*N* = 16)	Savolitinib + itraconazole (*N* = 15)	Savolitinib (*N* = 16)	Savolitinib + famotidine (2 h) (*N* = 16)	Midazolam (*N* = 14)	Midazolam + savolitinib (*N* = 14)
C_{max}, ng ml								
Gmean (gCV%)	2332 (26)	1044 (22)	757 (51)	794 (30)	2429 (24)	1913 (29)	3.9 (39)	3.2 (43)
[range]	[1500–3890]	[713–1420]	[289–2190]	[468–1230]	[1480–3780]	[1080–3350]	2–7	2–7
n	18	16	16	15	16	16	14	14
AUC, h.ng ml								
Gmean (gCV%)	12 810 (25)	4957 (16)	4008 (57)	4348 (41)	12 800 (32)	11 290 (31)	15 (39)	14 (36)
[range]	[6920–17 600]	[3860–6190]	[1270–8860]	[2300–8200]	[7360–23 200]	[5960–17 600]	[9–28]	[8–27]
n	17	11	13	14	16	15	12	13
$AUC_{(0\text{-}t)}$, h.ng ml								
Gmean (gCV%)	12 930 (25)	4866 (18)	3979 (50)	4319 (39)	12 760 (32)	11 200 (30)	14 (37)	13 (36)
[range]	[6880–17 600]	[3670–7170]	[1270–8850]	[2280–8150]	[7350–23 100]	[5940–17 500]	[8–26]	[8–26]
n	18	16	16	15	16	16	14	14
t_{max}, h								
Median	4.0	3.0	2.5	4.0	4.0	5.0	0.5	0.8
[range]	[1.5–6.1]	[1.5–8.0]	[0.5–6.0]	[1.0–5.0]	[0.5–5.0]	[1.5–6.0]	[0.3–2.0]	[0.2–3.0]
n	18	16	16	15	16	16	14	14
$t_{½\lambda z}$, h								
Mean ± SD	7.1 ± 1.6	7.0 ± 3.9	4.2 ± 1.6	4.6 ± 1.9	6.0 ± 2.4	5.9 ± 1.7	3.3 ± 1.4	3.3 ± 1.2
[range]	[4.2–10.0]	[1.9–11.5]	[2.7–7.9]	[2.8–8.7]	[2.4–10.0]	[2.4–8.1]	[1.6–6.7]	[1.9–6.0]
n	17	11	13	14	16	15	12	13
CL/F, L/h								
Mean ± SD	48.3 ± 12.9	122.4 ± 18.9	57.4 ± 35.5	49.4 ± 19.1	49.0 ± 15.1	55.5 ± 17.6	71.5 ± 25.4	73.6 ± 24.0
[range]	[34.0–86.7]	[96.9–156.0]	[22.6–157.0]	[24.4–87.1]	[25.9–81.6]	[34.0–101.0]	[35.6–115]	[36.8–118]
n	17	11	13	14	16	15	12	13

(Continues)

TABLE 2 (Continued)

	Rifampicin study		Itraconazole study		Famotidine study		Midazolam study	
	Savolitinib (*N* = 18)	Savolitinib + rifampicin (*N* = 16)	Savolitinib (*N* = 16)	Savolitinib + itraconazole (*N* = 15)	Savolitinib (*N* = 16)	Savolitinib + famotidine (2 h) (*N* = 16)	Midazolam (*N* = 14)	Midazolam + savolitinib (*N* = 14)
Vz/F, L								
Mean ± SD	506.2 ± 237.7	1246 ± 763.4	310.3 ± 148.9	323.9 ± 200.6	399.1 ± 161.8	443.2 ± 117.2	314.8 ± 108.9	324.6 ± 92.4
[range]	[222–1250]	[331–2300]	[182–742]	[167–906]	[227–730]	[256–648]	[167–516]	[188–461]
n	17	11	13	14	16	15	12	13

AUC, area under plasma concentration–time curve from time zero to infinity; $AUC_{(0\text{-}t)}$, area under the plasma concentration–time curve from time zero to time of last quantifiable concentration; CL/F, apparent total body clearance of drug from plasma after extravascular administration (parent drug only); C_{max}, maximum observed plasma concentration; gCV%, geometric coefficient of variation; Gmean, geometric mean; *n*, number of datapoints included in the summary statistics; *N*, number of volunteers in the pharmacokinetic analysis set; SD, standard deviation; $t_{½}\lambda z$, half-life associated with terminal slope (λz) of a semi-logarithmic concentration time curve; t_{max}, time to reach maximum observed plasma concentration; TP, treatment period; Vz/F, apparent volume of distribution during the terminal phase after extravascular administration (parent drug only).

Rifampicin study: TP1 (Days 1–14): savolitinib 600 mg once daily on Day 1; TP2 (Days 15–19): rifampicin 600 mg once daily on Days 15–19; TP3 (Days 20–22): savolitinib 600 mg once daily on Day 20 and rifampicin 600 mg once daily on Days 20 and 21; follow-up to Day 34.

Itraconazole study: TP1 (Days 1–14): savolitinib 200 mg once daily on Day 1; TP2 (Days 15–17): itraconazole 200 mg twice daily on Day 15 and itraconazole 200 mg once daily on Days 16 and 17; TP3 (Days 18–20): savolitinib 200 mg once daily on Day 18 and itraconazole 200 mg once daily on Days 18 and 19; follow-up to Day 32.

Famotidine study: on Day −1, volunteers were randomised 1:1 to either one of the two treatment sequences: single treatment (single oral dose of 600 mg savolitinib on Day 1) first followed by the combination treatment (single oral doses of 40 mg famotidine + 600 mg savolitinib on Day 16), or the reverse sequence, in TP1 and TP2; follow-up to Day 30.

Midazolam study: TP1 (Days −1–4): midazolam 1 mg once daily on Day 1; TP2 (Days 5–6): midazolam 1 mg once daily and savolitinib 600 mg once daily on Day 5; follow-up to Day 19.

(81.4–100.0) when savolitinib was dosed in combination with rifampicin compared with when dosed alone (Appendix Table A4). Although the overall mean C_{max} values for M2 and AUC values for M2/M3 were lower when savolitinib was dosed in combination with rifampicin, metabolite-to-parent C_{max} ratios for M2 and M3 increased by approximately 38.7% and 208.2%, and AUC ratios increased by 41.9% and 181.5%, respectively (Appendix Tables A1–A4; Appendix Figures A2A and A3A).

3.4 | Itraconazole study

The PK analysis set included 16 volunteers; one volunteer had available data for TP1 only due to early withdrawal from the study due to an important protocol deviation (positive screen for drug abuse of cotinine and/or alcohol). Exposure to savolitinib, based on geometric mean C_{max} and AUC, was similar when savolitinib was dosed in combination with itraconazole compared with savolitinib alone. The GMRs (% [90% CIs]) for C_{max}, AUC and $AUC_{(0\text{-}t)}$ were 105.2 (87.7–126.3), 108.4 (96.3–122.1) and 108.9 (98.5–120.5), respectively (Figure 2B, Table 3); no statistically significant difference was observed between the treatments (the 90% CI encompasses 100%). Exposure to M2, based on geometric mean C_{max} and AUC was similar, while $AUC_{(0\text{-}t)}$ was higher when savolitinib was dosed in combination with itraconazole compared with savolitinib alone; the M2 GMRs (% [90% CIs]) for C_{max}, AUC and $AUC_{(0\text{-}t)}$ were 104.9 (96.1–114.4), 111.6 (92.2–135.0) and 106.7 (102.0–111.7), respectively (Appendix Table A3; Appendix Figure A2B). Exposure to M3, based on geometric mean C_{max}, was similar, while $AUC_{(0\text{-}t)}$ was higher when savolitinib was dosed in combination with itraconazole compared with savolitinib alone; the M3 GMRs (% [90% CIs]) were 96.2 (84.8–109.1) and 111.2 (104.0–119.1), respectively (Appendix Table A4; Appendix Figure A3B). The median t_{max} for savolitinib, M2 and M3 levels when savolitinib was dosed in combination with itraconazole compared with when dosed alone was longer by 1.5 h (4.0 *vs* 2.5), 1.0 h (4.0 *vs* 3.0) and 1.5 h (4.0 *vs* 2.5), respectively. The metabolite-to-parent ratios for M2 and M3 exposure were similar for both treatments.

3.5 | Famotidine study

The PK analysis set included 16 volunteers; all of whom completed treatment. The GMRs (% [90% CIs]) for savolitinib in combination with famotidine (2 h earlier) compared with savolitinib when dosed alone were 78.8 (67.7–91.7), 87.4 (81.2–94.2) and 87.7 (81.8–94.1), respectively, for the C_{max}, AUC and $AUC_{(0\text{-}t)}$ of savolitinib (Table 3). M2 C_{max} was lower by 14% (76.0–96.3); AUC and $AUC_{(0\text{-}t)}$ were similar when savolitinib was dosed with famotidine (2 h earlier) compared with savolitinib when dosed alone (Appendix Table A3; Appendix Figure A2C). M3 C_{max}, AUC and $AUC_{(0\text{-}t)}$ were lower by 17% (73.6–94.5), 8% (87.3–97.8) and 7% (87.3–99.2), respectively,

TABLE 3 Statistical comparison of key pharmacokinetic parameters of savolitinib or midazolam, as appropriate (pharmacokinetic analysis set)

						Pairwise comparison			
Parameter (unit)	**Treatment**	***N***	***n***	**Geometric LS mean**	**95% CI**	***n***	**Pair**	**Geometric mean ratio (%)**	**90% CI**
C_{max} (ng ml)	Savolitinib	18	18	2332	[2064–2635]	16	Savolitinib + rifampicin/savolitinib	45.4	[41.4–49.9]
	Savolitinib + rifampicin	18	16	1059	[933–1203]				
	Savolitinib	16	16	757	[611–937]	15	Savolitinib + itraconazole/savolitinib	105.2	[87.7–126.3]
	Savolitinib + itraconazole	16	15	796	[640–991]				
	Savolitinib	16	16	2429	[2117–2786]	16	Savolitinib + famotidine (2 h) /savolitinib	78.8	[67.7–91.7]
	Savolitinib + famotidine (2 h)	16	16	1913	[1668–2195]				
	Midazolam	14	14	4	[3–5]	14	Midazolam + savolitinib/	84.1	[70.0–101.0]
	Midazolam + savolitinib	14	14	3	[3–4]		Savolitinib		
AUC (ng.h ml)	Savolitinib	18	17	12 810	[11 400–14 380]	10	Savolitinib + rifampicin/savolitinib	38.5	[34.2–43.3]
	Savolitinib + rifampicin	18	11	4932	[4292–5667]				
	Savolitinib	16	13	4010	[3063–5249]	13	Savolitinib + itraconazole/savolitinib	108.4	[96.3–122.1]
	Savolitinib + itraconazole	16	14	4348	[3330–5677]				
	Savolitinib	16	16	12 800	[10 850–15 100]	15	Savolitinib + famotidine (2 h) /savolitinib	87.4	[81.2–94.2]
	Savolitinib + famotidine (2 h)	16	15	11 190	[9477–13 220]				
	Midazolam	14	12	15	[12–18]	12	Midazolam + savolitinib/savolitinib	96.7	[92.4–101.1]
	Midazolam + savolitinib	14	13	14	[12–18]				
$AUC_{(0\text{-}t)}$ (ng.h ml)	Savolitinib	18	18	12 930	[11 590–14 430]	16	Savolitinib + rifampicin/savolitinib	37.8	[34.8–41.0]
	Savolitinib + rifampicin	18	16	4883	[4358–5472]				
	Savolitinib	16	16	3979	[3164–5003]	15	Savolitinib + itraconazole/savolitinib	108.9	[98.5–120.5]
	Savolitinib + itraconazole	16	15	4334	[3440–5461]				
	Savolitinib	16	16	12 760	[10 830–15 030]	16	Savolitinib + famotidine (2 h) /savolitinib	87.7	[81.8–94.1]
	Savolitinib + famotidine (2 h)	16	16	11 200	[9506–13 190]				
	Midazolam	14	14	14	[11–17]	14	Midazolam + savolitinib/savolitinib	96.1	[92.0–100.3]
	Midazolam + savolitinib	14	14	13	[11–16]				

AUC, area under plasma concentration–time curve from time zero to infinity; $AUC_{(0\text{-}t)}$, area under the plasma concentration–time curve from time zero to time of last quantifiable concentration; CI, confidence interval; C_{max}, maximum observed plasma concentration; LS, least squares; *n*, all volunteers included in the statistical comparison analysis; *N*, number of volunteers in the pharmacokinetic analysis set; PK, pharmacokinetic.

Rifampicin study: result based on analysis of variance of log-transformed PK parameter with fixed effect for treatment and random effect for volunteer.

Itraconazole study: result based on analysis of variance (ANOVA) of log-transformed PK parameter with fixed effect for treatment and random effect for volunteer.

Famotidine study: results are based on ANOVA of log-transformed PK parameter with sequence, period and treatment as fixed effect, and volunteer nested within sequence as random effect.

Midazolam study: result based on ANOVA of log-transformed PK parameter with a fixed effect for treatment and a random effect for volunteer.

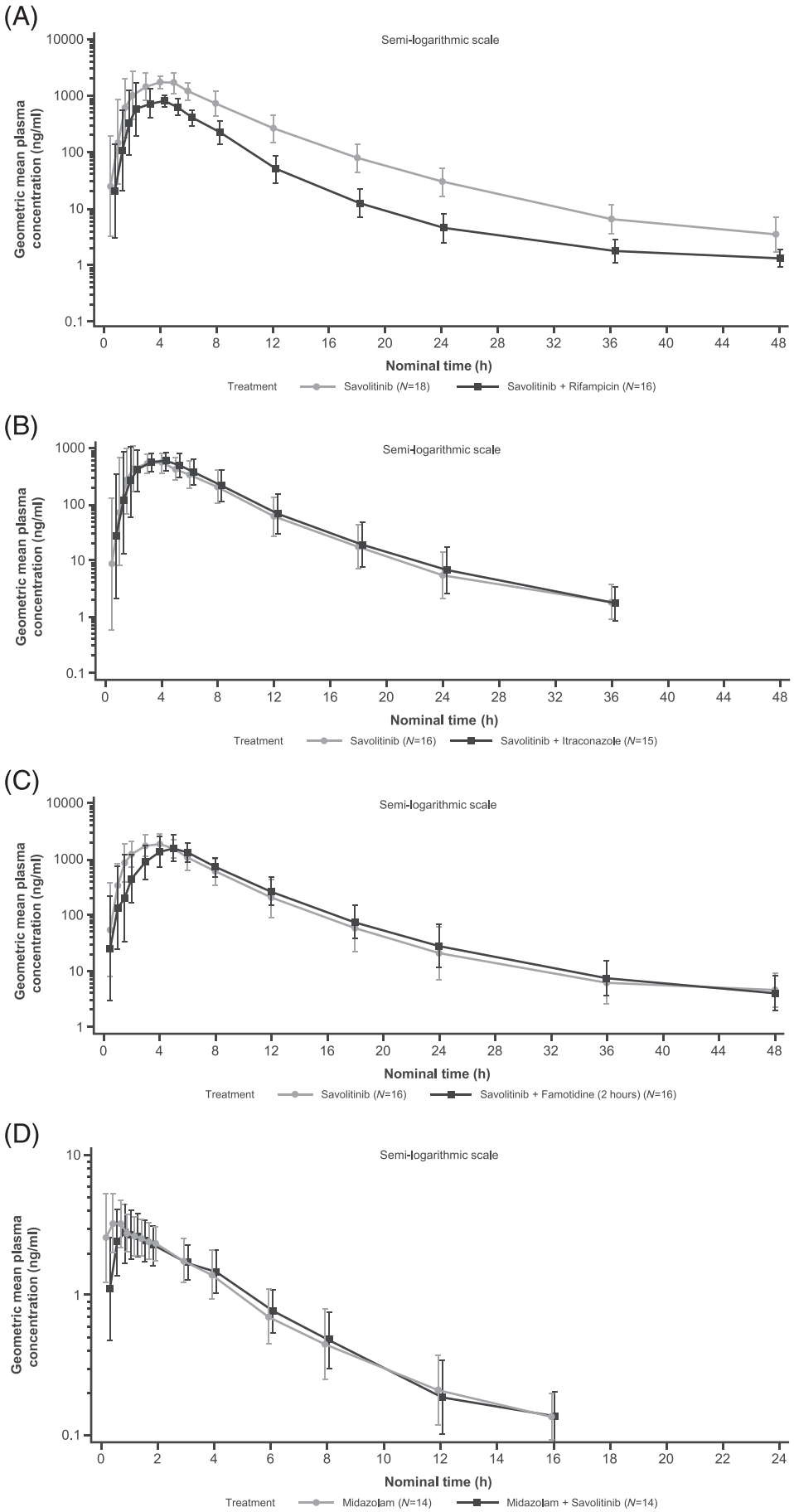


FIGURE 2 Geometric mean (± gSD) savolitinib plasma concentration–time profiles for (A) savolitinib ± rifampicin, (B) savolitinib ± itraconazole (C) savolitinib ± famotidine and (D) midazolam plasma–time profile for midazolam ± savolitinib (semi-logarithmic scale; pharmacokinetic analysis set)

when savolitinib was dosed with famotidine (2 h earlier), compared with savolitinib when dosed alone (Appendix Table A4; Appendix Figure A3C). The metabolite-to-parent ratios for M2 and M3 were similar for both treatments. Co-dosing of famotidine with savolitinib reduced exposure to savolitinib compared with savolitinib monotherapy, although this was not considered clinically meaningful. The differences in C_{max}, AUC and $AUC_{(0\text{-}t)}$ for savolitinib dosed with famotidine (2 h earlier) compared with savolitinib dosed alone did not exceed a 30% decrease for savolitinib (or both metabolites); thus, Part B of the study was not required as per the pre-specified criteria.

3.6 | Midazolam study

The PK analysis set included 14 volunteers, all of whom completed TP1/TP2. Exposure to midazolam, based on geometric mean C_{max}, AUC and $AUC_{(0\text{-}t)}$, was similar when dosed in combination with savolitinib compared with when dosed alone; the GMRs (% [90% CIs]) for C_{max}, AUC and $AUC_{(0\text{-}t)}$ were 84.1 (70.0–101.0), 96.7 (92.4–101.1) and 96.1 (92.0–100.3), respectively (Table 3). The median midazolam t_{max} was delayed by 0.25 h when midazolam was dosed in combination with savolitinib compared with midazolam alone. When midazolam was dosed in combination with savolitinib, C_{max} and AUC (gCV%) were 596 (35.0) and 4214 (36.1) for M2, and 205 (35.4) and 1485 (48.8) for M3, respectively (Appendix Tables A1 and A2); median t_{max} was 4.0 h for savolitinib, M2 and M3 (Appendix Tables A1–A4; Appendix Figure A2D).

3.7 | Safety

Savolitinib was well tolerated when administered alone or in combination with all study drugs in healthy, adult male volunteers. Overall, 55% (11/20), 38% (6/16), 38% (6/16) and 50% (7/14) of volunteers in the rifampicin, itraconazole, famotidine and midazolam studies, respectively, reported at least one treatment-emergent AE (Table 4).

In the rifampicin study, more volunteers reported AEs during TP2 (QD dosing of rifampicin 600 mg for 5 days) (56%; 10/18) than in the other two TPs. In total, 15% (3/20) of volunteers had AEs related to savolitinib and 45% (9/20) had AEs related to rifampicin; this included one volunteer with increased transaminases reported as related to both savolitinib and rifampicin. The most frequently reported AEs were chromaturia (45%; 9/20) and diarrhoea (10%; 2/20); all of which were reported during TP2. Headache was reported by 15% (3/20) of volunteers during TP1–TP2. One volunteer had a moderate AE of hypersensitivity during TP1 (single dose of savolitinib 600 mg), which led to discontinuation of the investigational treatment and withdrawal from the study.

In the itraconazole study, AEs were reported in TP1 (single dose of savolitinib 200 mg) and TP3 (single dose of savolitinib 200 mg and QD dosing of itraconazole 200 mg for 2 days) (13% [2/16] and 33% [5/15] of volunteers, respectively). The only AE reported by more than one volunteer was upper respiratory tract infection (19%; 3/16) during TP3. All other AEs, including diarrhoea, dyspepsia, stomatitis, headache and cough, were each reported by 6% (1/16) of volunteers; both cases of cough and stomatitis were considered related to itraconazole. There were no AEs considered as related to savolitinib.

In each treatment group in the famotidine study, (savolitinib 600 mg alone and savolitinib in combination with famotidine 40 mg) 19% (3/16) of volunteers reported at least one AE; in total, 38% (6/16) of volunteers across the two treatment groups experienced an AE. The most common AEs were increased transaminases and headache, both reported by 13% (2/16) of volunteers; all cases of which were reported in volunteers receiving savolitinib alone. Overall, 19% (3/16) of volunteers had an AE related to savolitinib; there were no AEs considered as related to famotidine.

In the midazolam study, AEs were reported by 36% (5/14) and 21% (3/14) of volunteers during TP1 (single dose of midazolam 1 mg) and TP2 (single dose of midazolam 1 mg in combination with single dose of savolitinib 600 mg), respectively; one volunteer had AEs in both TPs. AEs related to midazolam in TP1 were reported by 21% (3/14) of volunteers, of which 14% (2/14) reported somnolence and 7% (1/14) reported abdominal pain/headache. No volunteers had AEs related to savolitinib and/or midazolam in TP2.

Across all studies, there were no serious AEs and the majority of AEs were mild in intensity.

4 | DISCUSSION

Savolitinib is a MET-TKI which is currently being evaluated for treatment of various cancers either as monotherapy or in combination with other agents including osimertinib or durvalumab. It is important to understand the potential DDIs of savolitinib as it is highly likely to be co-administered with other agents in patients with advanced cancer requiring treatment for other comorbidities. We conducted four PK studies based on what was seen from *in vitro* data to determine the effect of concomitant therapy on savolitinib exposure and savolitinib on concomitant medication exposure. Rifampicin as a strong CYP3A inducer, itraconazole as a strong CYP3A4 inhibitor, famotidine as a gastric pH modifier and midazolam as a CYP3A4 substrate were chosen for clinical evaluation. As CYP3A inhibition could increase savolitinib exposure, the itraconazole study was conducted with a savolitinib 200 mg dose, while the rifampicin, famotidine and midazolam studies were conducted with savolitinib 600 mg, as the effects with rifampicin and famotidine were likely to lower the exposure of savolitinib when co-administered, while exposure was expected to increase when co-dosed with itraconazole; thus, preventing any safety concerns to healthy volunteers due to increased exposure.

When midazolam was dosed in combination with savolitinib compared with midazolam alone, PK parameters (C_{max}, AUC and $AUC_{[0\text{-}t]}$) were similar, with all 90% CIs encompassing unity. The PK exposure of savolitinib (in combination with midazolam) in the midazolam study (Table 2) was similar to the exposure of savolitinib observed in the famotidine or rifampicin studies when dosed alone; furthermore, the ranges in exposure appear to overlap compared to previous studies, even though the mean exposure is slightly

TABLE 4 Summary of all adverse events

n (%)	Rifampicin study (*N* = 20)	Itraconazole study (*N* = 16)	Famotidine study (*N* = 16)	Midazolam study (*N* = 14)
Volunteer with any TEAE	11 (55)	6 (38)	6 (38)	7 (50)
Chromaturia	9 (45)	0	0	0
Headache	3 (15)	1 (6)	2 (13)	3 (21)
Upper respiratory tract infection	0	3 (19)	0	0
Somnolence	0	0	0	2 (14)
Transaminases increased	1 (5)	0	2 (13)	0
Diarrhoea	2 (10)	1 (6)	0	0
Abdominal pain	0	0	0	1 (7)
Application site erythema	0	0	0	1 (7)
Contusion	0	0	0	1 (7)
Upper-airway cough syndrome	0	0	0	1 (7)
Dyspepsia	0	1 (6)	0	0
Stomatitis	0	1 (6)	0	0
Cough	0	1 (6)	0	0
Fatigue	0	0	1 (6)	0
Hordeolum	0	0	1 (6)	0
Burn oral cavity	0	0	1 (6)	0
Dermatitis	0	0	1 (6)	0
Acne	1 (5)	0	0	0
Nausea	1 (5)	0	0	0
Dizziness	1 (5)	0	0	0
Catheter site pain	1 (5)	0	0	0
Hypersensitivity	1 (5)	0	0	0

AE, adverse event; MedDRA, Medical Dictionary for Regulatory Activities; *N*, number of volunteers in the safety analysis set; %, number of volunteers in each category expressed as a percentage of *N*; TEAE, treatment-emergent adverse event; TP, treatment period.
Number (%) of volunteers with AEs, sorted by preferred term in decreasing order of frequency (sorted by total number on AstraZeneca investigational product).
MedDRA version 22.1. A volunteer could have one or more preferred terms reported under a given system organ class. AEs counted in more than one period for a given volunteer were counted once in total.
Rifampicin study: TP1 (Days 1–14): savolitinib 600 mg once daily on Day 1; TP2 (Days 15–19): rifampicin 600 mg once daily on Days 15–19; TP3 (Days 20–22): savolitinib 600 mg once daily on Day 20 and rifampicin 600 mg once daily on Days 20 and 21; follow-up to Day 34.
Itraconazole study: TP1 (Days 1–14): savolitinib 200 mg once daily on Day 1; TP2 (Days 15–17): itraconazole 200 mg twice daily on Day 15 and itraconazole 200 mg once daily on Days 16 and 17; TP3 (Days 18–20): savolitinib 200 mg once daily on Day 18 and itraconazole 200 mg once daily on Days 18 and 19; follow-up to Day 32.
Famotidine study: on Day −1, volunteers were randomised 1:1 to either one of the two treatment sequences: single treatment (single oral dose of 600 mg savolitinib on Day 1) first followed by the combination treatment (single oral doses of 40 mg famotidine + 600 mg savolitinib on Day 16), or the reverse sequence, in TP1 and TP2; follow-up to Day 30.
Midazolam study: TP1 (Days −1–4): midazolam 1 mg once daily on Day 1; TP2 (Days 5–6): midazolam 1 mg once daily and savolitinib 600 mg once daily on Day 5; follow-up to Day 19.

lower.[6,8] Moreover, the metabolite-to-parent ratios for both M2 and M3 were similar across these studies, indicating that their contribution to the interaction has also been evaluated; this suggests that the exposure of savolitinib and its metabolites, M2 and M3, was sufficient to evaluate the effect on midazolam in this study. Our results indicate that co-administration of midazolam with savolitinib has no effect on midazolam PK and thereby, on the CYP3A4 pathway. The midazolam study was designed to understand the single-dose effect of savolitinib and not at the steady state to confirm any potential effect on CYP3A induction. However, osimertinib (a CYP3A substrate) has shown no change in its exposure when co-administered with savolitinib, suggesting that there is low clinical potential for CYP3A induction by savolitinib.[7]

For famotidine, a previous study indicated that maximum clinical effect is achieved between 1 and 3 h (median 2 h) post-dose and is maintained for at least 10 h after the same 40 mg dose used in this

study (94% inhibition of nocturnal gastric acid secretion).[14] Thus, famotidine dosed 2 h earlier than savolitinib is likely to elicit maximal gastric pH change similar to that observed with proton pump inhibitors (PPIs). Despite the longer duration of effect with PPIs compared to H2RAs, a single dose study with H2RA is sufficient for maximal gastric pH change as seen with PPIs. Therefore, considering that savolitinib absorption is rapid, this study was able to provide an understanding of the effect of gastric pH change on savolitinib exposure. Here, co-administration of famotidine with savolitinib reduced exposure to savolitinib compared with savolitinib monotherapy, although this was not considered clinically meaningful. Furthermore, M2 and M3 C_{max} and M3 AUC and $AUC_{(0\text{-}t)}$ were lower when savolitinib was dosed with famotidine, compared with savolitinib dosed alone, whilst M2 AUC and $AUC_{(0\text{-}t)}$ were similar. The decreases seen when savolitinib was dosed with famotidine (2 h earlier) compared with savolitinib alone were greater for C_{max} than those for AUC and $AUC_{(0\text{-}t)}$. This is consistent with the slower rate of absorption of savolitinib as indicated by a later median t_{max} and having a greater impact on peak concentration (C_{max}) than on the overall extent of exposure (AUC) when dosed in the presence of famotidine compared to when dosed alone.

In these clinical studies, co-dosing of itraconazole or famotidine with savolitinib and of savolitinib with midazolam had no clinically significant effect on savolitinib or midazolam PK. Co-dosing of rifampicin reduced exposure to savolitinib compared with savolitinib monotherapy.

The presence of multiple elimination pathways for savolitinib may explain the lack of significant effect of itraconazole co-administration; rifampicin, however, is considered a pleiotropic inducer of multiple pregnane X receptor-inducible drug-metabolising enzymes, including CYP3A4, UGT and transporters[19] and this pleiotropic effect may contribute to savolitinib clearance, resulting in decreased exposure. In the rifampicin study, there was a decrease in AUC and C_{max} of savolitinib, and both clearance and volume of distribution were higher without any change in half-life in combination with rifampicin compared to savolitinib alone. This may suggest that the effect with rifampicin could primarily be due to the increased first pass metabolism; this is supported by the higher metabolite-to-parent ratios for M2 and M3 when savolitinib is dosed in combination with rifampicin compared to when dosed alone. Moreover, as the metabolism of savolitinib is increased by the induction of CYP, UGT and transporter enzymes by rifampicin, savolitinib exposure is decreased and the formation of metabolite M3 and to some extent, M2, is likely increased. The significant increase in M3 when savolitinib was dosed in combination with rifampicin could be due to the formation rate of M3 being considerably greater than the elimination rate, thereby leading to an increased concentration, while that might not be the case for M2. Overall, the C_{max} of M3 was higher (37.97%) and the AUC was slightly lower (8.16%) when savolitinib was dosed in combination with rifampicin compared to alone; the increase in C_{max} of M3 with rifampicin is not likely to be of any clinical significance.

Thus, our results indicate that CYP3A4 inhibitors have no clinically significant effect on savolitinib exposure and, hence, can be dosed with savolitinib; however, co-administration of savolitinib with potent CYP3A4 inducers decreases savolitinib exposure and should be avoided where possible.

There were few limitations with these studies as they implemented standard study designs; furthermore, no protocol deviations impacted the PK and there was at least the minimum number of volunteers that each study required to estimate the DDI effect. Nevertheless, it was not always possible to capture the AUC statistical inter-volunteer comparison for all analytes in all volunteers due to limitations in sampling and/or lower sensitivity for analysis in the terminal phase. Despite this, $AUC_{(0\text{-}t)}$ and C_{max} were well captured and there was a suitable representation. Whilst there was no measure of famotidine, rifampicin or gastric pH in these studies, this is a standard approach and is already well recognised in previous studies. Finally, though all four DDI studies enrolled healthy, male volunteers only, savolitinib exposure does not appear to be influenced by gender and the exposure of savolitinib appears to be similar in cancer patients and healthy volunteers [data on file].

5 | CONCLUSION

In conclusion, co-administration of famotidine and itraconazole with savolitinib had no clinically relevant PK effects on savolitinib exposure; thus, savolitinib may be co-administered with gastric acid modifiers or CYP3A inhibitors. Rifampicin in combination with savolitinib significantly reduced exposure of savolitinib compared with when dosed alone; thus, co-administration of potent CYP3A4 inducers with savolitinib should be avoided. Finally, co-administration of savolitinib with midazolam had no clinically significant effect on midazolam PK; thus, savolitinib may be combined with CYP3A substrates. Savolitinib alone or in combination with midazolam, famotidine, rifampicin or itraconazole demonstrated an acceptable safety profile in healthy, adult male volunteers and there were no new safety concerns observed.

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COMPETING INTERESTS

S.R., K.V., P.F., I.H., G.S., S.S. and Y.L. are employees of AstraZeneca and report ownership of stocks or shares in AstraZeneca. M.C. is a

contracted employee of AstraZeneca and reports ownership of stocks or shares in AstraZeneca. W.B. is an employee of Covance, a member of the PK Group, which analysed the PK data reported in this manuscript. D.H. is an employee of California Clinical Trial Medical Group in affiliation with Parexel, Inc. and reports receiving payment from Parexel, Inc. R.G. has no conflict of interest to report.

CONTRIBUTORS

Conceptualization: S.R., M.C., P.F., G.S., S.S. and R.G. Methodology: S.R., K.V., M.C., P.F., G.S., W.B. and S.S. Validation: Y.L. Formal analysis: S.R., M.C., P.F., I.H. and W.B. Investigation: K.V., D.H. and R.G. Resources: Y.L. Data curation and visualization: S.R. and K.V. Supervision: S.R., K.V., M.C., S.S. and R.G. Project administration: D.H. Drafting the manuscript: S.R., K.V., M.C., P.F., I.H., G.S., W.B., S.S., Y.L., D.H. and R.G. All authors critically reviewed the manuscript and approved the final version for submission.

DATA AVAILABILITY STATEMENT

The data underlying the findings described in this manuscript may be obtained in accordance with AstraZeneca's data sharing policy described at https://astrazenecagrouptrials.pharmacm.com/ST/Submission/Disclosure

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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