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 Cmax, 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...
alone and in combination with savolitinib for \(C_{\text{max}}\), 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

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### 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.\(^3,4\)

Single-dose savolitinib is rapidly absorbed with a relatively short time to peak \((t_{\text{max}})\) (around 2–4 hours\([h]\)); the maximum plasma concentration \((C_{\text{max}})\) 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), \(C_{\text{max}}\) 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 \((t_{\text{1/2}\lambda z})\) 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) \((\text{data on file})\) (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 \((\text{MDCK})\) cells with the MDR1 gene, savolitinib is a P-glycoprotein \((\text{P-gp})\) 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

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### 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.
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.\textsuperscript{9} Therefore, we sought to quantify the effect of the potent CYP3A4 enzyme and transporter inducer, *rifampicin*\textsuperscript{11} and the CYP3A4 and P-gp inhibitor, *itraconazole*,\textsuperscript{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.\textsuperscript{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.\textsuperscript{14}

A recent clinical study with savolitinib showed that a high fat meal increased AUC by approximately 18\%, while *C*\textsubscript{max} remained unchanged.\textsuperscript{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,\textsuperscript{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.\textsuperscript{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).

## 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*\textsubscript{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*\textsubscript{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
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-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-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-t}, t_{max} and half-life associated with terminal slope (1/2) of a semi-logarithmic concentration–time curve (t_{1/2}) 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-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
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/m². 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 $C_{\text{max}}$ 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 $C_{\text{max}}$, AUC and $AUC_{(0-t)}$ 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 $C_{\text{max}}$ 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, $C_{\text{max}}$ increased by 40% (124.9–156.8) and $AUC_{(0-t)}$ decreased by 10%
|                         | Rifampicin study | Itraconazole study | Famotidine study | Midazolam study |
|-------------------------|------------------|--------------------|------------------|----------------|
|                         | Savolitinib (N = 18) | Savolitinib + rifampicin (N = 16) | Savolitinib (N = 16) | Savolitinib + famotidine (2 h) (N = 16) |
| **C_{max}, ng ml**      |                  |                    |                  |                  |
| Gmean (gCV%)            | 2332 (26)        | 1044 (22)          | 757 (51)         | 794 (30)         |
| [range]                 | [1500–3890]      | [713–1420]         | [289–2190]       | [468–1230]       |
| **n**                   | 18               | 16                 | 16               | 15              |
| **AUC, h.ng ml**        |                  |                    |                  |                  |
| Gmean (gCV%)            | 12 810 (25)      | 4957 (16)          | 4008 (57)        | 4348 (41)        |
| [range]                 | [6920–17 600]    | [3860–6190]        | [1270–8860]      | [2300–8200]      |
| **n**                   | 17               | 11                 | 13               | 14              |
| **AUCl(0-t), h.ng ml**  |                  |                    |                  |                  |
| Gmean (gCV%)            | 12 930 (25)      | 4866 (18)          | 3979 (50)        | 4319 (39)        |
| [range]                 | [6880–17 600]    | [3670–7170]        | [1270–8850]      | [2280–8150]      |
| **n**                   | 18               | 16                 | 16               | 15              |
| **t_{max}, h**          |                  |                    |                  |                  |
| Median                  | 4.0              | 3.0                | 2.5              | 4.0             |
| [range]                 | [1.5–6.1]        | [1.5–8.0]          | [0.5–6.0]        | [1.0–5.0]        |
| **n**                   | 18               | 16                 | 16               | 15              |
| **t_{1/2}, h**          |                  |                    |                  |                  |
| Mean ± SD               | 7.1 ± 1.6        | 7.0 ± 3.9          | 4.2 ± 1.6        | 4.6 ± 1.9        |
| [range]                 | [4.2–10.0]       | [1.9–11.5]         | [2.7–7.9]        | [2.8–8.7]        |
| **n**                   | 17               | 11                 | 13               | 14              |
| **CL/F, L/h**           |                  |                    |                  |                  |
| Mean ± SD               | 48.3 ± 12.9      | 1224 ± 18.9        | 57.4 ± 35.5      | 49.4 ± 19.1      |
| [range]                 | [34.0–86.7]      | [96.9–156.0]       | [22.6–157.0]     | [24.4–87.1]      |
| **n**                   | 17               | 11                 | 13               | 14              |
TABLE 2

|          | Rifampicin study | Itraconazole study | Famotidine study | Midazolam study |
|----------|------------------|--------------------|------------------|----------------|
| Savolitinib | 314.8 ± 108.9   | 324.6 ± 94.4       | 310.3 ± 148.9   | 323.9 ± 200.6 |
| Savolitinib + rifampicin | 399.1 ± 16.1     | 443.2 ± 117.2     | 323.9 ± 148.9   | 443.2 ± 117.2 |
| Savolitinib + itraconazole | 2300 ± 742        | 1250 ± 331        | 182 ± 720       | 648 ± 167   |
| Midazolam | 314.8 ± 108.9   | 324.6 ± 94.4       | 310.3 ± 148.9   | 323.9 ± 200.6 |
| Gmean    | (N=14)          | (N=14)             | (N=14)          | (N=14)        |

Vz/F, L

506.2 ± 237.7 1246 ± 763.4 323.9 ± 200.6 323.9 ± 200.6

Mean ± SD

[range] – 1250 [331 2300] [182 720] [648 167]

n

17 16 15 15

108.9 (98.5–20.5), 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_C(0–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_C(0–t) were 105.2 (87.7–126.3), 108.4 (96.3–122.1) and 108.9 (98.5–20.5), respectively (Appendix Table A3; Appendix Figure A2B).

Exposure to M3, based on geometric mean C_max was similar, while AUC_C(0–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_C(0–t) of savolitinib (Table 3).

M2 C_max was lower by 14% (76.0–96.3); AUC and AUC_C(0–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_C(0–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)

| Parameter (unit)       | Treatment                  | N  | n  | Geometric LS mean | 95% CI          | Pairwise comparison |
|------------------------|----------------------------|----|----|-------------------|-----------------|---------------------|
|                        |                            |    |    |                   |                 | n       | Pair                     | Geometric mean ratio (%) | 90% CI               |
| $C_{\text{max}}$ (ng ml) | Savolitinib                | 18 | 18 | 2332              | [2064–2635]     | 16      | Savolitinib + rifampicin | 45.4                    | [41.4–49.9]           |
|                        | Savolitinib + rifampicin  | 18 | 16 | 1059              | [933–1203]      |          |                        |                         |                      |
|                        | Savolitinib                | 16 | 16 | 757               | [611–937]       | 15      | Savolitinib + itraconazole | 105.2                   | [87.7–126.3]          |
|                        | Savolitinib + itraconazole| 16 | 15 | 796               | [640–991]       |          |                        |                         |                      |
|                        | Savolitinib                | 16 | 16 | 2429              | [2117–2786]     | 16      | Savolitinib + famotidine (2 h) | 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]           |          |                        |                         |                      |
| $\text{AUC (ng.h ml)}$ | Savolitinib                | 18 | 17 | 12 810            | [11 400–14 380] | 10      | Savolitinib + rifampicin | 38.5                    | [34.2–43.3]           |
|                        | Savolitinib + rifampicin  | 18 | 13 | 4932              | [4292–5667]     |          |                        |                         |                      |
|                        | Savolitinib                | 16 | 14 | 4010              | [3063–5249]     | 13      | Savolitinib + itraconazole | 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) | 87.4                    | [81.2–94.2]           |
|                        | Savolitinib + famotidine (2 h) | 16 | 15 | 11 190            | [9477–13 220]   |          |                        |                         |                      |
|                        | Midazolam                  | 14 | 13 | 15                | [12–18]         | 12      | Midazolam + savolitinib | 96.7                    | [92.4–101.1]          |
|                        | Midazolam + savolitinib    | 14 | 13 | 14                | [12–18]         |          |                        |                         |                      |
| $\text{AUC}_{(0-\text{t})}$ (ng.h ml) | Savolitinib                | 18 | 18 | 12 930            | [11 590–14 430] | 16      | Savolitinib + rifampicin | 37.8                    | [34.8–41.0]           |
|                        | Savolitinib + rifampicin  | 18 | 16 | 4883              | [4358–5472]     |          |                        |                         |                      |
|                        | Savolitinib                | 16 | 16 | 3979              | [3164–5003]     | 15      | Savolitinib + itraconazole | 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) | 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 | 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; $\text{AUC}_{(0-\text{t})}$, area under the plasma concentration–time curve from time zero to time of last quantifiable concentration; CI, confidence interval; $C_{\text{max}}$, 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 $C_{\text{max}}$, AUC and $AUC_{0-d}$ 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 $C_{\text{max}}$, AUC and $AUC_{0-d}$, was similar when dosed in combination with savolitinib compared with when dosed alone; the GMRs (% [90% CIs]) for $C_{\text{max}}$, AUC and $AUC_{0-d}$ 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 $t_{\text{max}}$ 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, $C_{\text{max}}$ 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 $t_{\text{max}}$ 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, (somalitinib 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 of 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 ($C_{\text{max}}$, AUC and $AUC_{0-d}$) 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
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

### 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                         |                          |
| 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                          | 1 (6)                       | 0                         | 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.
that might not be the case for M2. Overall, the metabolism of savolitinib is increased by the induction of CYP, with rifampicin compared to when dosed alone. Moreover, as parent ratios for M2 and M3 when savolitinib is dosed in combination with rifampicin were higher without any change in half-life in combination with savolitinib compared with savolitinib monotherapy, although this was not considered clinically meaningful. Furthermore, M2 and M3 $C_{\text{max}}$ and M3 AUC and $AUC(0-t)$ were lower when savolitinib was dosed with famotidine, compared with savolitinib dosed alone, whilst M2 AUC and $AUC(0-t)$ were similar. The decreases seen when savolitinib was dosed with famotidine (2 h earlier) compared with savolitinib alone were greater for $C_{\text{max}}$ than those for AUC and $AUC(0-t)$. This is consistent with the slower rate of absorption of savolitinib as indicated by a later median $t_{\text{max}}$ and having a greater impact on peak concentration ($C_{\text{max}}$) 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 and this pleiotropic effect may contribute to savolitinib clearance, resulting in decreased exposure. In the rifampicin study, there was a decrease in AUC and $C_{\text{max}}$ 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 of 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 $C_{\text{max}}$ 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 $C_{\text{max}}$ 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, $AUC(0-t)$ and $C_{\text{max}}$ 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.

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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. 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/SubmissionDisclosure

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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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