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ORIGINAL ARTICLE

Effect of a strong CYP3A4 inhibitor and inducer on the pharmacokinetics of senaparib (IMP4297) in healthy volunteers: A drug–drug interaction study

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Aims: A phase I open-label study assessed the effect of multiple oral doses of a potent CYP3A4 inhibitor (itraconazole) and inducer (rifampicin) on the pharmacokinetic profile of a single oral dose of senaparib, a novel, highly potent poly-(ADP-ribose) polymerase 1/2 inhibitor and CYP3A4 substrate, in Chinese healthy male volunteers (HMV).

Methods: Adult HMV were enrolled to the itraconazole or rifampicin group ($n = 16$ each). In Period 1, all participants received a single oral dose of senaparib 40 mg (itraconazole group) or 100 mg (rifampicin group). In Period 2, the same dose was coadministered with itraconazole (200 mg) and rifampicin (600 mg), respectively. The primary endpoints were senaparib exposure parameters.

Results: Coadministration with itraconazole significantly increased exposure of senaparib and decreased that of its major metabolites M9 and M14. Maximum plasma senaparib concentration (C_{max}) was increased by ~79% and area under the concentration–time curve (AUC) increased by ~2.8-fold. Coadministration with rifampicin significantly reduced the C_{max} and AUC of senaparib by ~59 and 83%, respectively. The C_{max} for both M9 and M14 was slightly increased, although AUC was decreased. All treatment-emergent adverse events were grade ≤2, regardless of the treatment administered.

Conclusion: In Chinese HMV, the exposure of senaparib was significantly increased when coadministered with itraconazole and significantly decreased when coadministered with rifampicin. It is recommended to avoid concomitant use of senaparib and strong inhibitors or inducers of CYP3A4.

KEYWORDS
cytochrome P450, drug interactions, drug metabolism, drug safety, pharmacokinetics; pharmacovigilance, phase I; anticancer drugs

1 | INTRODUCTION

Poly-(ADP-ribose) polymerase (PARP) inhibitors are a class of precision anticancer therapy that target PARP1 and PARP2 in the DNA

The authors confirm that the Principal Investigator for this work is Professor Pingsheng Xu of Xiangya Hospital, Central South University, Changsha, China, and that Professor Xu had direct clinical responsibility for the study volunteers.

damage repair pathway and selectively kill tumours that are homologous-recombination repair (HRR) deficient.[1,2] PARP inhibition leads to stalling of DNA single-strand break repair and consequent formation and accumulation of DNA double-strand breaks. In healthy cells, these would be repaired via the high-fidelity HRR pathway, key components of which are the breast cancer susceptibility proteins BRCA1 and BRCA2. In HRR-deficient tumours, such as those with mutations in *BRCA1* and *BRCA2* (BRCAm), an error-prone repair pathway is activated, resulting in genome fragmentation and cell death.[1–4] BRCAm predispose to the development of several types of malignancy, and BRCAm tumours are sensitive to PARP inhibition.[2,4,5] Approval of several PARP inhibitors has improved outcomes for patients with a variety of solid tumour types; however, 40–70% of patients do not respond,[2,6,7] and more options are needed.

Senaparib (formerly IMP4297) is a novel and highly potent oral PARP(1/2) inhibitor that has demonstrated strong preclinical antitumour activity and approximately 20-fold greater potency (on a molar basis) than olaparib, which is the most well-developed of currently approved PARP inhibitors.[8–10] Pharmacokinetic (PK) data from 2 phase I in-human trials of senaparib in patients with advanced solid tumours conducted in Australia and China (NCT03507543; NCT03508011) revealed that senaparib is rapidly absorbed, demonstrates little accumulation and possesses dose-dependent exposure kinetics in the dose range 2–80 mg (plasma exposure increased proportionally in the dose range 2–80 mg and appeared to reach a plateau at 80–150 mg). In addition, senaparib demonstrated promising clinical benefit and a favourable safety profile.[9,11] The recommended phase II dose for senaparib monotherapy was determined to be 100 mg, administered once daily (QD).

Polypharmacy is common among cancer patients, putting them at risk for clinically significant drug–drug interactions.[12] The family of cytochrome P450 (CYP) enzymes is heavily involved in the metabolism of xenobiotics in humans, catalysing the oxidative biotransformation of many of these compounds. The 3A4 isoform (CYP3A4), the most abundantly expressed CYP enzyme (mainly in the liver and gastrointestinal tract), has a broad substrate specificity and can accommodate and oxidize multiple large molecules simultaneously. CYP3A4 plays a major role in the first-pass metabolism of many orally administered drugs, including targeted anticancer drugs.[13–16] Upon absorption from the intestinal lumen or hepatic parenchyma, drugs that are metabolized by CYP3A4 may be rapidly transformed via oxidation into their metabolites, thus reducing the bioavailability of the active drug within the circulation.[17] Agents that inhibit or are dependent upon CYP metabolism are especially likely to cause drug–drug interactions, potentially resulting in significantly altered clearance of both the drug and its metabolites, and negatively impacting drug safety and efficacy.[12,15] CYP3A4 is the main metabolic enzyme of senaparib, the major active metabolites of which were found through preclinical studies to be M9 and M14 (unpublished data on file, IMPACT Therapeutics [Shanghai] Inc., Shanghai, China). Therefore, the present study was conducted to assess the effect of a strong CYP3A4 inhibitor (itraconazole) and inducer (rifampicin)[18] on the PK characteristics of senaparib and its active metabolites (M9 and M14) after a single oral dose in healthy male volunteers (HMV) in China.

What is already known about this subject

- Poly-(ADP-ribose) polymerase inhibitors have improved outcomes for patients with homologous-recombination-repair-deficient tumours.
- Senaparib (IMP4297), a novel, potent poly-(ADP-ribose) polymerase 1/2 inhibitor, has demonstrated promising clinical antitumour activity.
- The pharmacokinetic effects of a strong CYP3A4 inhibitor (itraconazole) and inducer (rifampicin) on senaparib, a CYP3A4 substrate, are unclear.

What this study adds

- In Chinese healthy male volunteers, senaparib exposure was significantly increased by coadministration with itraconazole, and decreased by coadministration with rifampicin.
- A single dose of senaparib, alone or coadministered with itraconazole/rifampicin, was well tolerated in healthy male volunteers.
- Simultaneous administration of senaparib with strong inhibitors or inducers of CYP3A4 should be avoided.

2 | METHODS

2.1 | Trial design and subjects

A phase I, open-label study was conducted in China with the primary objective of assessing the effect of multiple oral doses of itraconazole and rifampicin on the PK profile of a single oral dose of senaparib in HMV (NCT04584515). Secondary objectives were to assess the safety and tolerability of a single oral dose of senaparib alone and when coadministered with itraconazole (hereafter senaparib + itraconazole) or rifampicin (hereafter senaparib + rifampicin) in HMV.

HMV aged 18–55 years with a body mass index of 19.0–26.0 kg/m^2 and body weight ≥50 kg were enrolled. HMV with a corrected QT interval (according to Fridericia's formula) from a resting 12-lead electrocardiogram (ECG) of >450 ms or QRS complex >120 ms were ineligible. A full account of the inclusion and exclusion criteria is provided in the Supporting Information (Section 1.1).

Two parallel groups of HMV (itraconazole group and rifampicin group) were enrolled and assigned to receive study treatments in a fixed sequence over 2 treatment periods: senaparib alone (Period 1)

and senaparib coadministration (Period 2; Figure 1). In Period 1, HMV received a single 40-mg (itraconazole group) or 100-mg (rifampicin group) dose of senaparib on Day (D)1. In Period 2, the itraconazole group received itraconazole (200 mg) QD from D5 to D13; on D10 they received a single 40-mg dose of senaparib 1 h prior to their daily itraconazole dose. In the rifampicin group, subjects received rifampicin (600 mg) QD from D5 to D17; on D14 they received a single 100-mg dose of senaparib with their daily rifampicin dose. Per their respective labels, subjects took rifampicin in a fasted state and itraconazole immediately after a full meal.[19,20] Senaparib was taken in a fasted state (i.e., at the same time as rifampicin and 1 h before itraconazole). This decision was based on a recently completed food-effect study (NCT04057729; data not yet published), which demonstrated no significant food effect on exposure parameters, thus indicating that senaparib can be administered with or without food. The rationale underlying the choice of dosing and treatment schedules for senaparib, itraconazole and rifampicin is provided in the Supporting Information (Section 1.2).

This study had institutional independent ethics committee approval and was conducted according to the ethical principles of the Declaration of Helsinki, ICH Harmonised Tripartite Guideline: Guideline for Good Clinical Practice and the applicable laws and regulations of China. All subjects provided written informed consent to participate before undergoing any study procedures.

2.2 | Assessments

2.2.1 | PK

In both treatment periods, blood samples for PK measurements of senaparib and its major metabolites M9 and M14 were collected within 1 h before administration of senaparib alone or before coadministration with itraconazole (D10) or rifampicin (D14), and then at 0.5 h ± 1 min, 1 h ± 3 min, 1.5 h ± 3 min, 2 h ± 6 min, 2.5 h ± 6 min, 3 h ± 6 min, 4 h ± 10 min, 5 h ± 10 min, 6 h ± 10 min, 8 h ± 20 min, 10 h ± 30 min, 12 h ± 30 min, 24 h ± 1 h, 48 h ± 2 h, 72 h ± 3 h and 96 h ± 4 h after senaparib administration (Figure 1). All blood samples were centrifuged at approximately 1700 × *g* for about 10 min at 4°C. The obtained plasma samples were stored in a freezer at approximately −70°C until required for bioanalysis. Plasma concentrations of senaparib, M9 and M14 were measured using a validated liquid chromatography–tandem mass spectrometry method at Quintiles Medical Research Co., Ltd. (Beijing, China). All the samples were analysed within an established long-term stability period (371 days). The lower limit of quantitation for determination of plasma concentrations was 5 ng/mL for senaparib and 2 ng/mL for both M9 and M14. The total number of PK samples and samples above the lower limit of quantitation at each time point were summarized. When at least 1 concentration measure at a time point was below the limit of quantitation (BLQ), the geometric mean and geometric coefficient of variation (CV%) were not reported for descriptive statistics at that time point. When ≥50% of the concentration data at a single time point were BLQ, the mean value at that time point was reported as 0.

2.2.2 | Safety

Treatment-emergent adverse events (TEAEs) were recorded from the time of the first dose of senaparib until 30 days after the last dose. Laboratory testing, vital signs, physical examination and ECG were assessed at admission (D −1) and at regular intervals until discharge (Supporting Information: Section 1.3 and Table S1).

2.3 | Study endpoints

The primary endpoints were maximum plasma concentration of senaparib (C_{max}), area under the plasma concentration–time curve (AUC) from time 0 to the time of the last quantifiable concentration

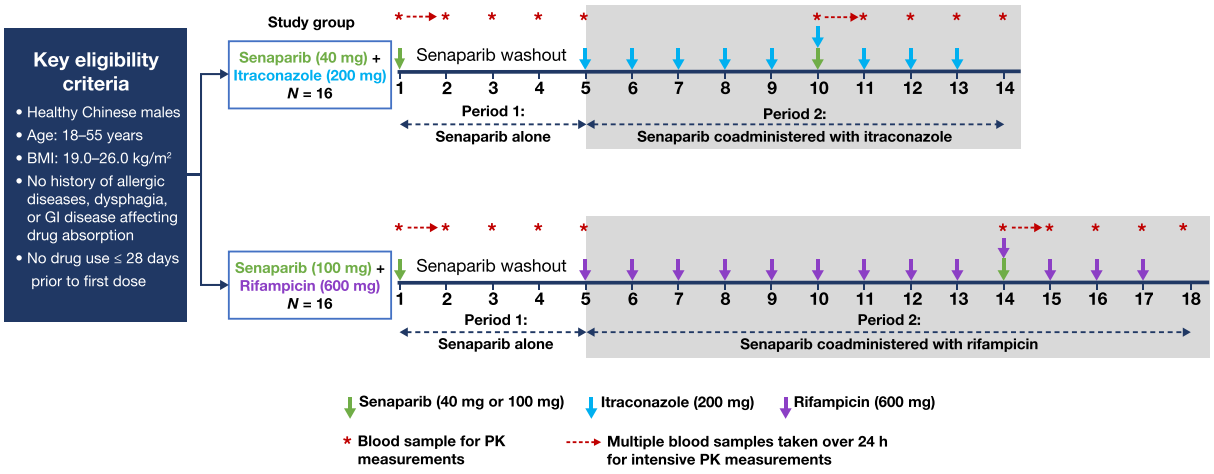

FIGURE 1 IMP4297-104 drug–drug interaction study design: effect of coadministration of senaparib with itraconazole or rifampicin, compared with senaparib alone, on the pharmacokinetic profile of senaparib in Chinese healthy male volunteers. BMI, body mass index; GI, gastrointestinal; PK, pharmacokinetic

(AUC_{0-last}) and AUC from time 0 to infinity (AUC_{0-inf}). Secondary PK endpoints included time to reach C_{max} (T_{max}), terminal elimination half-life ($t_{½}$), apparent clearance (CL/F), apparent volume of distribution (V_z/F) and safety (TEAEs, laboratory tests, physical examination, vital signs and 12-lead ECG). Analyses of the PK parameters of the senaparib metabolites M9 and M14 were exploratory. Definitions of all PK parameters and methods used to calculate them are provided in the Supporting Information (Table S2).

2.4 | Statistical analysis

No statistical power considerations were used to determine the sample size for this study, which was calculated based on the estimation method. The 90% confidence interval (CI) and precision achieved by different ratios for AUC and C_{max} after administration of senaparib under the coadministration (test) and senaparib alone (reference) conditions were calculated using the assumption that at least 12 subjects in each group would complete the study. Assuming that the within-subject standard deviations are small (e.g., 0.15 and 0.2 for senaparib $\log_e$AUC and $\log_e C_{max}$, respectively), the corresponding precision is 11% for AUC and 15% for C_{max}. If the within-subject standard deviations are high (e.g., the corresponding within-subject standard deviation increases to 0.3 and 0.5, respectively), the corresponding precision is 22% for AUC and 36% for C_{max}. Allowing for a dropout rate of approximately 20%, it was determined that 16 subjects should be enrolled per treatment group. Baseline data were summarized for the full analysis set (all subjects who received ≥1 dose of study drug). Plasma concentration data for senaparib, M9 and M14 were summarized descriptively for the PK concentration set (all subjects who received ≥1 dose of senaparib and had ≥1 evaluable postdose concentration measure) in Periods 1 and 2 (Figure 1). PK parameters were analysed using noncompartmental analysis (Phoenix WinNonlin software; version 8.2, Certara USA, Princeton, NJ, USA) and summarized descriptively by group and treatment period for the PK parameter set (all subjects who received ≥1 dose of senaparib and had ≥1 evaluable PK parameter measurement for senaparib or its metabolites). Mixed-effects modelling was used to estimate differences in natural-log transformed exposure parameters (i.e., C_{max}, AUC_{0-last} and AUC_{0-inf}) between coadministration and senaparib alone, with presence or absence of drug coadministration as the fixed effect and subject as the random effect. Itraconazole and rifampicin were considered to have no effect on the exposure of senaparib or its metabolites if the 90% CIs for the ratios of adjusted geometric mean for C_{max}, AUC_{0-last} and AUC_{0-inf} (via exponential transformation) fell entirely within the equivalence acceptance range of 80.0–125%.[21] Safety data were analysed for all subjects who received ≥1 dose of senaparib and had postdose safety evaluation data.

Handling of missing data is described in the Supporting Information (Section 1.4, Table S3). All statistical analyses were conducted using SAS software (version 9.4, SAS Institute, Inc., Cary, NC, USA). For PK data, R software (version 3.6.3, R Core Team, R Foundation for Statistical Computing, Vienna, Austria) was also used for graphical presentation.

2.5 | Nomenclature statement

The drug and molecular target nomenclature used in this work conforms to the International Union of Basic and Clinical Pharmacology/British Pharmacological Society nomenclature classification.[22] 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.[22]

3 | RESULTS

3.1 | Subject disposition and baseline characteristics

The trial was completed by all 16 HMV enrolled in the itraconazole group and by 15 of the 16 HMV enrolled in the rifampicin group (1 subject withdrew prematurely due to poor compliance). All 16 subjects in both the itraconazole and rifampicin groups were included in the PK concentration set and PK parameter set; however, 1 subject in the rifampicin group withdrew from the study during Period 2 and was therefore excluded from the analysis of variance for comparing the 2 treatment periods. Sensitivity analyses confirmed that exclusion of the data from the subject who withdrew prematurely had no impact on the statistical analyses of the PK of senaparib or its metabolites. The demographic and baseline characteristics of the study participants were generally similar for the 2 treatment groups. Two exceptions were for smoking status and alcohol consumption: a higher proportion of HMV in the rifampicin group were never smokers (75.0 *vs.* 62.5%) or never drinkers (81.3 *vs.* 50.0%; Table 1).

3.2 | Compliance

The compliance rate was 100% for both treatment periods for the itraconazole group (all 16 subjects received all planned doses of senaparib and itraconazole). In the rifampicin group, compliance was 100% for Period 1 and 93.8% for Period 2 (15 subjects received all planned doses of senaparib and rifampicin; 1 subject received neither).

3.3 | PK analyses

3.3.1 | Itraconazole group

The plasma concentrations of senaparib were increased and its elimination rates decreased when coadministered with itraconazole compared with senaparib alone (Figure 2A,B). The PK parameters of senaparib, M9 and M14 following administration of senaparib alone or in combination with itraconazole are summarized in Table 2. The interindividual variability of exposure parameters (expressed as

TABLE 1 Summary of subject baseline and demographic characteristics (full analysis set)

Characteristic	Itraconazole group $n = 16$	Rifampicin group $n = 16$
Age, years, mean ± SD (range)	25.6 ± 5.8 (18–38)	25.5 ± 5.0 (18–33)
Sex, *n* (%)		
Male	16 (100)	16 (100)
Ethnicity, *n* (%)		
Han	15 (93.8)	15 (93.8)
Other	1 (6.3)	1 (6.3)
BMI, kg/m^2, mean ± SD (range)	22.2 ± 2.3 (19.2–25.6)	22.9 ± 1.5 (19.9–24.7)
Smoking status, *n* (%)		
Never	10 (62.5)	12 (75.0)
Occasional (≤5 cigarettes/day)	3 (18.8)	3 (18.8)
Regular	0	0
Quit for ≤3 months	1 (6.3)	0
Quit for >3 months	2 (12.5)	1 (6.3)
Alcohol consumption, *n* (%)		
Never	8 (50.0)	13 (81.3)
Occasional (≤14 units of alcohol/week)	7 (43.8)	2 (12.5)
Regular	0	0
Abstained for ≤3 months	1 (6.3)	0
Abstained for >3 months	0	1 (6.3)

BMI, body mass index; SD, standard deviation.

geometric CV%) was lower following senaparib + itraconazole than senaparib alone. The median T_{max} of senaparib was the same with or without itraconazole (1.5 h), and $t_{½}$ was prolonged following senaparib + itraconazole. As shown in Table 3 and Figure 3, the geometric mean ratios (coadministration/administration alone) for C_{max}, AUC_{0-last} and AUC_{0-inf} were 179, 378 and 376%, respectively; the corresponding 90% CIs fell outside the equivalence acceptance range of 80.0–125%. Coadministration with itraconazole increased the C_{max}, and AUC (for both AUC_{0-last} and AUC_{0-inf}) of senaparib by ~79% and ~2.8-fold, respectively.

The plasma concentrations of the active metabolite M9 were decreased and its elimination rate decreased following coadministration with itraconazole (Figure S1a,b). The $t_{½}$ of M9 was prolonged following senaparib + itraconazole (Table 2). The 90% CIs of geometric mean ratios for M9 exposure parameters also fell outside the equivalence acceptance range (Table 3). C_{max}, AUC_{0-last} and AUC_{0-inf} were reduced by ~77, ~53 and ~50%, respectively, following coadministration with itraconazole *vs*. senaparib alone (Table 2). In Period 1 (senaparib alone), the geometric mean C_{max} and AUC_{0-inf} of M9 were approximately 22.2 and 34.8% of senaparib values, respectively; in Period 2 (senaparib + itraconazole), these were markedly reduced to 2.83 and 4.72%, respectively, of those for senaparib (Table 2).

The plasma concentrations of another active metabolite, M14, were low in Period 1 and decreased further to BLQ in all but 1 subject in Period 2 (Supporting Information: Figure S2a,b). The geometric mean C_{max} of M14 was approximately 0.416 and 0.111% of senaparib values in Periods 1 and 2, respectively (Table 2). No statistical analysis was performed for M14 exposure given the low levels of that metabolite.

3.3.2 | Rifampicin group

The plasma concentrations of senaparib were decreased and its elimination rate increased when coadministered with rifampicin compared with senaparib alone (Figure 2C,D). The PK parameters of senaparib, M9 and M14 following administration of senaparib alone or in combination with rifampicin are summarized in Table 4. The interindividual variability (geometric CV%) of C_{max} was slightly higher following senaparib + rifampicin than senaparib alone, while geometric CV% values for AUC_{0-last} and AUC_{0-inf} were comparable. The median T_{max} of senaparib was 1.5 h with and without rifampicin. The $t_{½}$ was shortened following senaparib + rifampicin. As shown in Table 3 and Figure 3, the geometric mean ratios (coadministration/administration alone) for the C_{max}, AUC_{0-last} and AUC_{0-inf} of senaparib were 41.2,

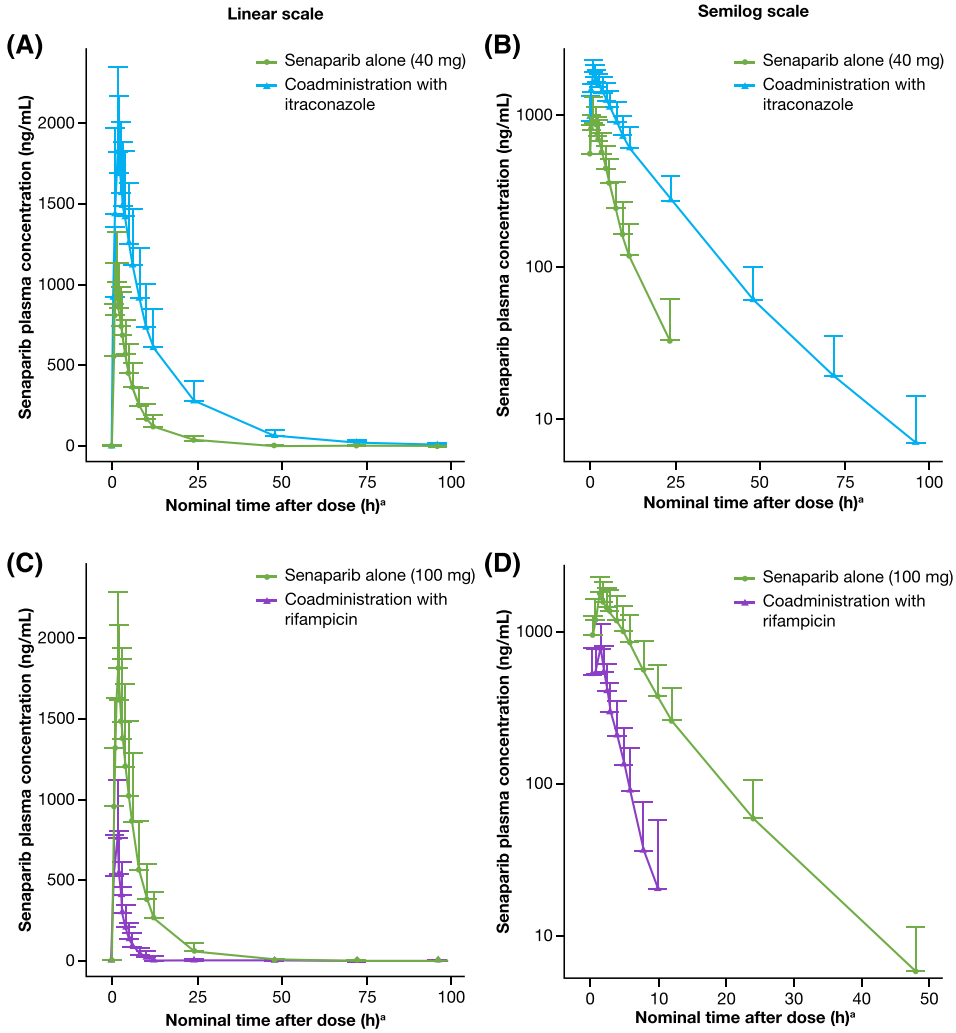

FIGURE 2 Linear and semilog plasma concentration–time curves for senaparib (A, B) after administration alone (40 mg) or coadministered with itraconazole (200 mg) and (C, D) after administration alone (100 mg) and coadministered with rifampicin (600 mg) in Chinese healthy male volunteers. When ≥50% of the concentration data at a single time point were defined as BLQ, the mean concentration at that time point was set to BLQ. BLQ data were set to 0 on the linear scale and are not presented on the semilog scale. Error bars represent standard deviation. [a] Nominal time after dose: planned sampling time postdose. BLQ, below the limit of quantification

17.3 and 17.4%, respectively; the corresponding 90% CIs fell outside the equivalence acceptance range. Coadministration with rifampicin decreased the C_{max} and AUC (for both AUC_{0-last} and AUC_{0-inf}) of senaparib by ~59 and ~83%, respectively.

Both the C_{max} and elimination rate of the active metabolite M9 were increased following coadministration with rifampicin (Supporting Information: Figure S1c,d). The 90% CIs of geometric mean ratios of M9 exposure parameters (C_{max} and AUC) fell outside the equivalence acceptance range (Table 3). Coadministration with rifampicin increased the C_{max} of M9 by ~64% but decreased the AUC (for both AUC_{0-last} and AUC_{0-inf}) by ~18%. In Period 1 (senaparib alone), the geometric mean C_{max} and AUC_{0-inf} of M9 were ~25.5 and ~37.9% of that for senaparib, respectively; in Period 2 (senaparib + rifampicin), these ratios were increased, with the M9 of C_{max} and AUC_{0-inf} being 101 and 180%, respectively, of those for senaparib (Table 4).

The plasma concentrations of another active metabolite, M14, were low in Period 1; the C_{max} was slightly increased and its elimination rate also increased in Period 2 (Supporting Information: Figure S2c,d). The 90% CIs of geometric mean ratios of M14 exposure parameters (C_{max}, AUC) fell outside the equivalence acceptance range (Table 3). Coadministration of rifampicin increased the C_{max} of M14 by ~10% and decreased the AUC_{0-last} by ~48%. In Period 1 (senaparib alone), the geometric mean C_{max} of M14 was 0.332% of that for senaparib, and the ratio for AUC_{0-inf} was not calculable; in Period 2 (senaparib + rifampicin), the geometric mean ratios of C_{max} and AUC_{0-inf} for M14 were increased to 0.882 and 2.05% of senaparib values, respectively (Table 4).

3.4 | Safety

Mean ± standard deviation exposure of senaparib in the itraconazole and rifampicin treatment groups was 80.0 ± 0.0 mg and 193.8 ± 25.0 mg, respectively, with a mean exposure duration of 2.0 ± 0.0 days for itraconazole and 1.9 ± 0.3 days for rifampicin. Mean exposure to itraconazole and rifampicin was 1800.0 ± 0.0 mg (mean exposure time, 9.0 ± 0.0 days) and 7650.0 ± 600.0 mg (mean exposure time, 12.8 ± 1.0 days), respectively.

TABLE 2 Summary of the key pharmacokinetic (PK) parameters of senaparib and its active metabolites M9 and M14 following administration of 40 mg senaparib alone or coadministered with itraconazole in Chinese healthy male volunteers[a]

Parent	Treatment period	C_{max} (ng/mL)	T_{max} (h)	AUC_{0-last} (ng·h/mL)	AUC_{0-inf} (ng·h/mL)	$t_{½}$ (h)	CL/F (L/h)	V_z/F (L)
Senaparib $n = 16$	1: Senaparib (40 mg) alone[b]	1020 (32.1%)	1.50 (0.50–1.50)	5590 (49.2%)	5500 (51.5%)	6.76 (46.2%)	7.27 (51.5%)	70.8 (46.3%)
	2: Senaparib (40 mg) + itraconazole (200 mg)	1820 (27.5%)	1.50 (1.00–2.00)	21 100 (39.6%)	21 300 (39.7%)	12.3 (29.9%)	1.88 (39.7%)	33.4 (25.4%)
Metabolites	**Treatment period**	**C_{max} (ng/mL)**	**T_{max} (h)**	**AUC_{0-last} (ng·h/mL)**	**AUC_{0-inf} (ng·h/mL)**	**$t_{½}$ (h)**	**MPratio_C_{max}**	**MPratio_AUC**
M9 $n = 16$	1: Senaparib (40 mg) alone[c]	233 (35.3%)	1.50 (1.50–3.00)	2010 (50.2%)	2030 (50.1%)	7.19 (36.3%)	0.222 (18.5%)	0.348 (16.6%)
	2: Senaparib (40 mg) + itraconazole (200 mg)[d]	53.3 (36.7%)	3.00 (1.51–6.00)	940 (55.5%)	1090 (50.2%)	12.2 (24.0%)	0.0283 (25.1%)	0.0472 (30.3%)
M14 $n = 16$	1: Senaparib (40 mg) alone[e]	4.35 (69.7%)	1.50 (1.00–6.00)	11.0 (85.1%)	NC	NC	0.00416 (65.8%)	NC
	2: Senaparib (40 mg) + itraconazole (200 mg)[f]	2.01	2.50	NC	NC	NC	0.00111	NC

λ_z, elimination rate constant; Adj_Rsq, adjusted coefficient of determination; AUC_{0-last}, area under the concentration–time curve from time 0 to the last quantifiable concentration; AUC_{0-inf}, area under the concentration–time curve from time 0 to infinity; CI, confidence interval; CL/F, apparent clearance; C_{max}, maximum plasma concentration; GCV%, geometric coefficient of variation; GM, geometric mean; MPratio_AUC, ratio of metabolite AUC_{0-inf} to parent drug AUC_{0-inf}; MPratio_C_{max}, ratio of metabolite C_{max} to parent drug C_{max}; NC, not calculable; SD, standard deviation; $t_{½}$, elimination half-life; T_{max}, time to C_{max}; V_z/F, apparent volume of distribution.

[a]PK parameters are presented as geometric mean (geometric coefficient of variation), with the exception of T_{max}, which is presented as median (range).

[b]In Period 1 the λ_z of 2 subjects could not be accurately calculated due to Adj_Rsq < 0.900, so the number of subjects with calculated parameters based on λ_z in this period was 14.

[c]The AUC_{0-inf} of 1 subject in Period 1 could not be accurately calculated and was not included in the statistical analysis.

[d]The AUC_{0-inf} of 2 subjects in Period 2 could not be accurately calculated and were not included in the statistical analysis.

[e]In Period 1, since λ_z could not be calculated or could not be accurately calculated for all subjects at this stage, the number of subjects included in the final descriptive statistical analysis for λ_z in this period and the parameters calculated based on λ_z during this period was 0, and the corresponding parameter was not included in the statistical analysis and is presented as NC.

[f]In Period 2, these PK parameters could be calculated only for a single subject, and thus individual values were listed and no descriptive statistical analysis was performed.

TABLE 3 Statistical analysis summary of the effect of coadministration of senaparib with itraconazole or rifampicin on the pharmacokinetic (PK) parameters of senaparib and its active metabolites M9 and M14, compared with senaparib administration alone in Chinese healthy male volunteers[a]

			Senaparib alone		Coadministration			
Plasma compound measured	**Combination treatment group**	**PK parameter**	***n***	**GM**	***n***	**GM**	**GM ratio[b] (90% CI)**	**Intraindividual CV**
Senaparib (parent)	**Senaparib (40 mg) + itraconazole (200 mg) *n* = 16**	C_{max} (ng/mL)	16	1020	16	1820	179% (164–196)	14.8
		AUC_{0-last} (ng·h/mL)	16	5590	16	21 100	378% (338–423)	18.2
		AUC_{0-inf} (ng·h/mL)	14[c]	5500	16	21 300	376% (330–427)	19.5
	Senaparib (100 mg) + rifampicin (600 mg) *n* = 16	C_{max} (ng/mL)	15[d]	1860	15[d]	766	41.2% (35.6–47.6)	22.9
		AUC_{0-last} (ng·h/mL)	15[d]	11 500	15[d]	2000	17.3% (14.9–20.1)	23.9
		AUC_{0-inf} (ng·h/mL)	15[d]	11 700	15[d]	2030	17.4% (14.9–20.3)	24.2
M9 (metabolite)	**Senaparib (40 mg) + itraconazole (200 mg) *n* = 16**	C_{max} (ng/mL)	16	233	16	53.3	22.9% (20.5–25.5)	17.8
		AUC_{0-last} (ng·h/mL)	16	2010	16	940	46.9% (41.4–53.1)	20.4
		AUC_{0-inf} (ng·h/mL)	15[e]	2030	14[f]	1090	50.1% (43.4–57.8)	21.0
	Senaparib (100 mg) + rifampicin (600 mg) *n* = 16	C_{max} (ng/mL)	15[d]	489	15[d]	800	164% (141–191)	24.0
		AUC_{0-last} (ng·h/mL)	15[d]	4550	15[d]	3740	82.1% (71.5–94.3)	21.8
		AUC_{0-inf} (ng·h/mL)	15[d]	4600	15[d]	3770	82.1% (71.5–94.2)	21.6
M14[g] (metabolite)	**Senaparib (100 mg) + rifampicin (600 mg) *n* = 16**	C_{max} (ng/mL)	15[d]	6.13	15[d]	6.72	110% (92.2–131)	27.6
		AUC_{0-last} (ng·h/mL)	15[d]	33.8	15[d]	17.5	51.7% (39.8–67.3)	42.7

AUC_{0-last}, area under the concentration–time curve from time 0 to the last quantifiable concentration; AUC_{0-inf}, area under the concentration–time curve from time 0 to infinity; CI, confidence interval; C_{max}, maximum plasma concentration; CV, coefficient of variation; GM, geometric mean.

[a]The values after logarithm transformation used PROC MIXED process to carry out analysis of variance. Coadministration or not was introduced into the model as a fixed effect, and individuals were introduced into the model as random effects.

[b]Ratio of coadministration *vs.* administration of senaparib alone.

[c]AUC_{0-inf} of 2 subjects in the senaparib alone period could not be accurately calculated and was not included in the statistical analysis.

[d]One subject was withdrawn from the study and only received treatment in Period 1 (senaparib alone); that subject was not included in this statistical analysis.

[e]AUC_{0-inf} of 1 subject in the senaparib alone period could not be accurately calculated and was not included in the statistical analysis.

[f]AUC_{0-inf} of 2 subjects in the coadministration period could not be accurately calculated and was not included in the statistical analysis.

[g]The low levels of M14 observed following administration of itraconazole precluded statistical analysis of exposure for this metabolite.

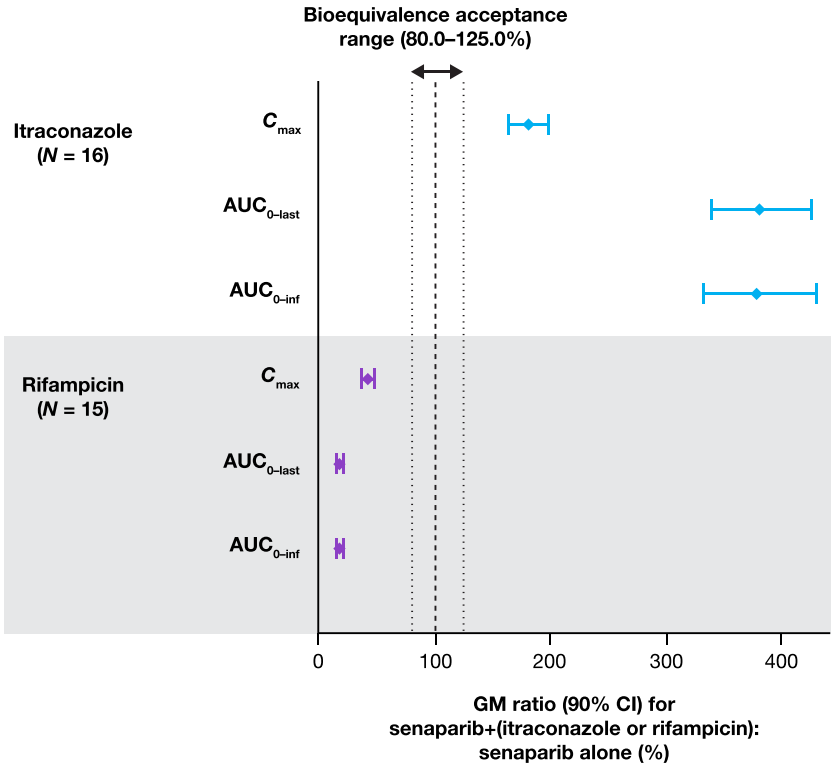

FIGURE 3 Forest plot of the effect of coadministration of senaparib with itraconazole or rifampicin compared with senaparib alone on the exposure parameters of senaparib in Chinese healthy male volunteers. AUC_{0-last}, area under the concentration–time curve from time 0 to the last quantifiable concentration; AUC_{0-inf}, area under the concentration–time curve from time 0 to infinity; CI, confidence interval; C_{max}, maximum plasma concentration; GM, geometric mean.

3.4.1 | TEAEs

There were no serious TEAEs, TEAEs grade ≥3 (per the National Cancer Institute Common Criteria for Adverse Events version 5.0[23]) or TEAEs leading to discontinuation of any of the study drugs or to death in either treatment group, regardless of the study period. In Period 1, 5 (31.3%) subjects in the itraconazole group experienced a total of 5 TEAEs, most commonly hypertriglyceridaemia ($n = 2$, 12.5%). Three TEAEs in 3 (18.8%) subjects were considered to be related to senaparib only: upper respiratory tract infection, blood glucose increase and total bile acid increase (Table 5). In Period 2, 5 (31.3%) subjects in this group reported 6 TEAEs. All 6 were considered to be related to both senaparib and itraconazole, as were 2 TEAEs of hypertriglyceridaemia in 2 subjects that began in Period 1 but worsened during Period 2 (Table 5). The most frequently occurring TEAE was increased bilirubin ($n = 3$, 18.8%). None of the TEAEs were related to itraconazole only. There were 2 grade 2 TEAEs (hypertriglyceridaemia and blood bilirubin increased); all others were grade 1. The grade 2 blood bilirubin increase resolved with concomitant medication. The outcome for 3 TEAEs (blood bilirubin increase, γ-glutamyltransferase increase and hypertriglyceridaemia) was unknown due to loss to follow-up; all other TEAEs ultimately resolved.

For the rifampicin group, 5 (31.3%) subjects reported a total of 7 TEAEs during Period 1, all hypertriglyceridaemia and all related to senaparib only (Table 5). One (6.3%) subject experienced 2 TEAEs, testicular pain and hypoaesthesia, both of which were believed to have begun in Period 1 but were judged by the investigator to be related to both senaparib and rifampicin. In Period 2, 3 (18.8%) subjects in the rifampicin group recorded 4 TEAEs, most commonly blood pressure increase ($n = 2$, 12.5%; Table 5). Both cases of blood pressure increase were considered related to rifampicin only. One (6.3%) subject experienced 2 TEAEs that were considered to be related to both senaparib and rifampicin: oropharyngeal pain and blood creatine phosphokinase increase. Grade 2 TEAEs of blood pressure increase ($n = 2$ subjects), hypertriglyceridaemia, hypoaesthesia and testicular pain ($n = 1$ subject each) were recorded; all others were grade 1. Concomitant medication was required to treat the subject with hypoaesthesia and testicular pain, and there was 1 case of elevated blood creatine kinase for which the outcome was unknown due to loss of follow-up; all other TEAEs resolved without sequelae.

3.4.2 | Other safety endpoints

In general, there were no significant differences in median values of changes in laboratory findings from baseline to the end of Period 1 and to the end of Period 2 in either treatment group. Any differences were small and returned to normal, or were abnormal but without clinical significance. Any clinically significant changes in laboratory findings, vital signs and physical examinations are listed in Table S4. No abnormal or clinically significant ECG changes were observed after administration of senaparib, whether alone or when coadministered with either itraconazole or rifampicin.

TABLE 4 Summary of the key pharmacokinetic (PK) parameters of senaparib and its active metabolites M9 and M14 following administration of 100 mg senaparib alone or coadministered with rifampicin in Chinese healthy male volunteers[a]

Parent	Treatment period	C_{max} (ng/mL)	T_{max} (h)	AUC_{0-last} (ng·h/mL)	AUC_{0-inf} (ng·h/mL)	$t_{½}$ (h)	CL/F (L/h)	V_z/F (L)
Senaparib	1: Senaparib (100 mg) alone	1830 (23.0%)	1.50 (1.00–2.50)	11 300 (45.0%)	11 500 (44.6%)	6.01 (26.8%)	8.72 (44.6%)	75.7 (41.9%)
$n = 16$[b]	2: Senaparib (100 mg) + rifampicin (600 mg)	766 (40.0%)	1.50 (0.50–1.51)	2000 (42.6%)	2030 (43.9%)	1.69 (28.0%)	49.3 (43.9%)	120 (47.1%)
Metabolites	**Treatment period**	**C_{max} (ng/mL)**	**T_{max} (h)**	**AUC_{0-last} (ng·h/mL)**	**AUC_{0-inf} (ng·h/mL)**	**$t_{½}$ (h)**	**MPratio_C_{max}**	**MPratio_AUC**
M9	1: Senaparib (100 mg) alone	481 (25.6%)	2.00 (1.00–4.00)	4440 (40.3%)	4490 (39.9%)	7.24 (21.4%)	0.255 (20.4%)	0.379 (20.2%)
$n = 16$[b]	2: Senaparib (100 mg) + rifampicin (600 mg)	800 (22.4%)	1.50 (1.00–2.50)	3740 (39.3%)	3770 (39.0%)	3.99 (23.1%)	1.01 (22.3%)	1.80 (15.9%)
M14	1: Senaparib (100 mg) alone	6.03 (26.8%)	1.50 (1.00–5.00)	33.2 (63.9%)	NC	NC	0.00332 (23.6%)	NC
$n = 16$[b]	2: Senaparib (100 mg) + rifampicin (600 mg)	6.72 (35.2%)	1.50 (1.00–2.00)	17.5 (50.5%)	39.7 (39.2–40.2)	1.96 (1.95–1.98)	0.00882 (43.1%)	0.0205 (0.0181, 0.0231)

AUC_{0-last}, area under the concentration–time curve from time 0 to the last quantifiable concentration; AUC_{0-inf}, area under the concentration–time curve from time 0 to infinity; CI, confidence interval; CL/F, apparent clearance; C_{max}, maximum plasma concentration; GCV%, geometric coefficient of variation; GM, geometric mean; MPratio_AUC, ratio of metabolite AUC_{0-inf} to parent drug AUC_{0-inf}; MPratio_C_{max}, ratio of metabolite C_{max} to parent drug C_{max}; NC, not calculable; SD, standard deviation; $t_{½}$, elimination half-life; T_{max}, time to C_{max}; V_z/F, apparent volume of distribution.

[a]PK parameters are presented as geometric mean (geometric coefficient of variation), with the exception of T_{max}, which is presented as median (range).

[b]One subject was withdrawn from the study in Period 2, and pharmacokinetic parameters could only be obtained during Period 1.

4 | DISCUSSION

The findings of this drug–drug interaction study demonstrate that strong CYP3A4 inhibition and induction altered the PK characteristics of senaparib in opposing directions in Chinese HMV. Despite this, both senaparib + itraconazole and senaparib + rifampicin were well tolerated, with only mild- to moderate-severity TEAEs being reported. These results should be taken into account by physicians when considering concomitant use of senaparib with strong inhibitors or inducers of CYP3A4 in oncology patients.

As expected given the demonstrated involvement of CYP3A4 in the in vitro metabolism of senaparib and production of its metabolites (unpublished data on file, IMPACT Therapeutics [Shanghai] Inc., Shanghai, China), coadministration of senaparib with the strong CYP3A4 inhibitor itraconazole[18] in HMV reduced the CL/F of senaparib and significantly increased its exposure compared with administration of senaparib alone. The C_{max} and AUC of senaparib increased by ~79% and ~2.8-fold, respectively. There was a concomitant reduction in exposure for its active metabolites (M9 and M14). The C_{max} and AUC of M9 were decreased by ~77 and ~50–53%, respectively, and plasma concentrations of M14 were decreased to BLQ in all but 1 patient following coadministration with itraconazole. This confirmed that CYP3A4 plays a role in the formation of these 2 senaparib metabolites. Moreover, the $t_{½}$ of M9 appeared to increase during coadministration with itraconazole, which suggests that CYP3A4 also mediates the metabolism of M9, which could be inhibited in the presence of itraconazole. It should be noted that as the exposure to M14 was very low in the presence or absence of itraconazole, the evaluation of its metabolic pathway is not applicable here. Since a significant increase in senaparib exposure may exacerbate any potential toxic side effects, it is recommended to avoid concomitant use of senaparib with strong CYP3A4 inhibitors such as itraconazole.

Also consistent with expectations, coadministration of the CYP3A4 substrate senaparib with the strong pan-inducer of CYP enzymes (including CYP3A4) rifampicin[18] increased the CL/F of senaparib in HMV, resulting in a clinically significant reduction in senaparib exposure compared with senaparib alone. The C_{max} and AUC of senaparib decreased by ~59 and ~83%, respectively, following coadministration with rifampicin. In addition, there was a slight decrease in the AUC of M9 (~18%), although the C_{max} of M9 was increased by ~64%; $t_{½}$ was also shortened. Similarly, there was a decrease in the AUC of M14 (~48%) although the C_{max} of M14 was slightly increased (~10%) following coadministration with rifampicin. The elimination rates of both M9 and M14 were increased following coadministration with rifampicin. Together with the findings from the interaction with itraconazole coadministration, this confirmed that the metabolism of M9, and possibly M14, is mediated through the CYP3A4 pathway, which could be induced in the presence of rifampicin. The clinically significant reduction in senaparib exposure observed following coadministration with rifampicin may negatively impact the efficacy of the PARP inhibitor, potentially causing treatment failure. Therefore, it is recommended

TABLE 5 Summary of treatment-emergent adverse events (TEAEs) reported with senaparib when administered alone (Period 1) and when coadministered with itraconazole and rifampicin, respectively (Period 2), and the most frequently reported in Chinese healthy male volunteers

	Itraconazole group $N = 16$				Rifampicin group $N = 16$			
	Period 1 Senaparib		Period 2 Senaparib + itraconazole		Period 1 Senaparib		Period 2 Senaparib + rifampicin	
TEAE summary	**Ev (*n*)**	***n* (%)**	**Ev (*n*)**	***n* (%)**	**Ev (*n*)**	***n* (%)**	**Ev (*n*)**	***n* (%)**
Any TEAE[a]	5	5 (31.3)	6	5 (31.3)	7	5 (31.3)	4	3 (18.8)
TEAEs related to senaparib	5	5 (31.3)	6	5 (31.3)	7	5 (31.3)	2	1 (6.3)
TEAEs related to CYP3A4 inhibitor/inducer	–	–	6	5 (31.3)	–	–	4	3 (18.8)

	Related to senaparib		Related to senaparib		Related to itraconazole		Related to senaparib		Related to senaparib		Related to rifampicin	
TEAEs by preferred term	**Ev (*n*)**	***n* (%)**	**Ev (*n*)**	***n* (%)**	**Ev (*n*)**	***n* (%)**	**Ev (*n*)**	***n* (%)**	**Ev (*n*)**	***n* (%)**	**Ev (*n*)**	***n* (%)**
Increased bilirubin	–	–	3	3 (18.8)[c]	3	3 (18.8)[c]	–	–	–	–	–	–
γ-Glutamyltransferase increased	–	–	1	1 (6.3)[c]	1	1 (6.3)[c]	–	–	–	–	–	–
Alanine aminotransferase increased	–	–	1	1 (6.3)[c]	1	1 (6.3)[c]	–	–	–	–	–	–
Total bile acids increased	1	1 (6.3)	–	–	–	–	–	–	–	–	–	–
Platelet count decreased	–	–	1	1 (6.3)[c]	1	1 (6.3)[c]	–	–	–	–	–	–
Blood glucose increased	1	1 (6.3)	–	–	–	–	–	–	–	–	–	–
Hypertriglyceridaemia	2	2 (12.5)[b]	–	–	–	–	5	5 (31.3)	–	–	–	–
Upper respiratory tract infection	1	1 (6.3)	–	–	–	–	–	–	–	–	–	–
Blood pressure increased	–	–	–	–	–	–	–	–	–	–	2	2 (12.5)
Blood creatine phosphokinase increased	–	–	–	–	–	–	–	–	1	1 (6.3)[d]	1	1 (6.3)[d]
Hypoaesthesia	–	–	–	–	–	–	1	1 (6.3)[e]	–	–	–	–
Oropharyngeal pain	–	–	–	–	–	–	–	–	1	1 (6.3)[d]	1	1 (6.3)[d]
Testicular pain	–	–	–	–	–	–	1	1 (6.3)[e]	–	–	–	–

Ev (*n*), number of events; *n* (%), number of patients (percentage of the treatment group).

[a]The following adverse events did not occur in either period with itraconazole: serious adverse events, TEAE grade ≥3; TEAE leading to discontinuation of senaparib (either dose), itraconazole or rifampicin; TEAE leading to withdrawal from the trial; TEAE leading to death.

[b]Two patients each experienced hypertriglyceridaemia that was first reported in Period 1 and considered to be related to senaparib; however, they were slightly aggravated after the subjects entered Period 2. The investigator judged that this hypertriglyceridaemia was related to both senaparib and itraconazole and included it in the TEAEs related to both senaparib and itraconazole.

[c]In each patient, this TEAE was considered to be related to both senaparib and itraconazole.

[d]In each patient, this TEAE was considered to be related to both senaparib and rifampicin.

[e]One subject had 2 TEAEs of left-testicular pain and hypoaesthesia; the start date after imputation was in Period 1; however, these 2 TEAEs were judged by the investigator to be related to both senaparib and rifampicin, so the events were not counted as TEAEs related to rifampicin in Period 2.

to avoid concomitant use of senaparib with strong CYP3A4 inducers like rifampicin.

Overall, the safety data demonstrated that a single dose of senaparib alone or coadministered with a strong CYP3A4 inhibitor or inducer was well tolerated in Chinese HMV. Coadministration of senaparib with itraconazole/rifampicin did not significantly increase the incidence of TEAEs or their severity at the dose levels used. There were no unexpected TEAEs related to senaparib alone; all were grade 1–2 and none were serious. All TEAEs resolved, with the exception of 4 TEAEs in 3 subjects who were lost to follow-up. Two subjects experienced blood pressure increase that was attributed to rifampicin alone. Hypertension does not appear in the US Food and Drug Administration (FDA) package insert for rifampicin.[19] With that exception, there were no unexpected TEAEs for either itraconazole or rifampicin.

Of note, 7 subjects experienced grade 1 hypertriglyceridaemia during Period 1, 2 in the itraconazole group and 5 in the rifampicin group. Senaparib + itraconazole increased the severity of hypertriglyceridaemia to grade 2. In the rifampicin group, however, the condition appeared to be resolved by coadministration with rifampicin in all subjects, potentially due to rifampicin-induced reduced exposure to senaparib. Hypertriglyceridaemia is a known rare side effect of itraconazole.[19] The present PK data suggest that the observed hypertriglyceridaemia in the itraconazole group may be attributable largely to the increased exposure of both itraconazole and senaparib.

Four PARP inhibitors (olaparib, niraparib, rucaparib and talazoparib) are currently approved by the FDA for the treatment of 1 or more of BRCAm or HRR-gene-mutated ovarian, breast, pancreatic and prostate cancer. Two of these PARP inhibitors, rucaparib and olaparib, are metabolized by CYP enzymes.[8,24] Olaparib, like senaparib, is metabolized by CYP3A4 and is known to both inhibit and induce CYP3A and to induce CYP2B6.[8] In patients with advanced solid tumours, olaparib exposure was significantly increased by coadministration with itraconazole and significantly decreased by coadministration with rifampicin. The safety profile was as expected for olaparib.[25] On the basis of these findings, the FDA prescribing information advises that olaparib should not be taken with strong or moderate CYP3A4 inhibitors or inducers.[8] While the PK data for senaparib appear similar to those for olaparib, direct comparison is challenging due to differences in the study populations (i.e., HMV *vs.* patients with advanced solid tumours). Deployment of HMV in the clinical PK profiling of noncytotoxic targeted oncology agents, including drug–drug interaction studies, is not only recognized by the FDA as an acceptable option, but is also considered advantageous (e.g., expediting the information required to inform subsequent clinical trials in patients; enabling enrolment of patients in those clinical trials who might otherwise have been excluded). Healthy female volunteers were not included in the study due to the known teratogenic and embryofoetal toxicity potential of PARP inhibitors.[8,24,26,27] However, a population PK analysis has demonstrated no sex differences in the PK characteristics of senaparib (unpublished data on file, IMPACT Therapeutics [Shanghai] Inc., Shanghai, China). The enrolment of HMV in the present study was considered appropriate and feasible based on the established good safety profile of senaparib in patients with advanced solid tumours (NCT03507543, NCT03508011), as well as in healthy volunteers included in a food-effect study (NCT04057729) and a bioequivalence study (NCT04351165). All the 4 studies were completed but not yet published at the time of writing (data on file, IMPACT Therapeutics [Shanghai] Inc., Shanghai, China). Phase II and III studies of senaparib in patients with BRCAm ovarian cancer are ongoing in China (NCT04089189 and NCT04169997, respectively).

The present findings should be considered in light of the small sample size, which did not allow definitive attribution of the causality of TEAEs or the establishment of any firm conclusions regarding the relationship between the safety profile and PK findings for senaparib. Further study is warranted in Phase II and III studies in patients, and with larger study populations.

The results of this study confirm that senaparib is a substrate of CYP3A4. Compared with senaparib alone, coadministration with the strong CYP3A4 inhibitor itraconazole in HMV significantly increased the C_{max} and AUC of senaparib, while clinically significant reductions were observed following coadministration with the strong CYP3A4 inducer rifampicin. It is therefore recommended that concomitant administration of senaparib with strong inhibitors or inducers of CYP3A4 should be avoided. Nonetheless, coadministration of a single dose of senaparib with a strong CYP3A4 inhibitor/inducer was well tolerated in Chinese HMV.

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COMPETING INTERESTS

C.Y.H., S.X.C., L.L., M.Z., H.S. and H.Z. are employees of IMPACT Therapeutics (Shanghai) Inc. The other authors have no conflicts of interest to declare.

CONTRIBUTORS

P.X., X.L., X.H., C.Y.H., S.X.C., L.L., M.Z., H.S., H.Z. and P.L. were involved in study design, data analysis and interpretation; Y.Z., W.L. and S.X. were involved in data analysis and interpretation. All authors critically reviewed the manuscript and approved the final draft.

PARTICIPANT CONSENT

Written informed consent to participate in this trial was provided by all enrolled participants.

CLINICAL TRIAL REGISTRATION

This trial is registered at ClinicalTrials.gov, ID: NCT04584515.

DATA AVAILABILITY STATEMENT

The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

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REFERENCES

1. Lord CJ, Ashworth A. PARP inhibitors: the first synthetic lethal targeted therapy. *Science*. 2017;355(6330):1152-1158. doi:10.1126/science.aam7344
2. Rose M, Burgess JT, O'Byrne K, Richard DJ, Bolderson E. PARP inhibitors: clinical relevance, mechanisms of action and tumor resistance. *Front Cell Dev Biol*. 2020;8:564601. doi:10.3389/fcell.2020.564601
3. Bryant HE, Schultz N, Thomas HD, et al. Specific killing of *BRCA2*-deficient tumours with inhibitors of poly (ADP-ribose) polymerase. *Nature*. 2005;434(7035):913-917. doi:10.1038/nature03443
4. Farmer H, McCabe N, Lord CJ, et al. Targeting the DNA repair defect in BRCA mutant cells as a therapeutic strategy. *Nature*. 2005;434(7035):917-921. doi:10.1038/nature03445
5. Fong PC, Boss DS, Yap TA, et al. Inhibition of poly (ADP-ribose) polymerase in tumors from BRCA mutation carriers. *N Engl J Med*. 2009;361(2):123-134. doi:10.1056/NEJMoa0900212
6. Jiang X, Li X, Li W, Bai H, Zhang Z. PARP inhibitors in ovarian cancer: sensitivity prediction and resistance mechanisms. *J Cell Mol Med*. 2019;23(4):2303-2313. doi:10.1111/jcmm.14133
7. Li H, Liu ZY, Wu N, Chen YC, Cheng Q, Wang J. PARP inhibitor resistance: the underlying mechanisms and clinical implications. *Mol Cancer*. 2020;19(1):107. doi:10.1186/s12943-020-01227-0
8. AstraZeneca Pharmaceuticals LP. LYNPARZA® (olaparib) tablets, for oral use. https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/208558s023lbl.pdf. Accessed January 3, 2022.
9. Xu B, Junning C, Guo H, et al. 577P Updated analysis of phase I dose-escalation and dose cohort expansion studies of senaparib (IMP4297) in Chinese patients with advanced solid tumours. Poster presented at the European Society of Medical Oncology Virtual Congress; 2020 September 19–21. *Cancer Res*. 2016;76(Suppl 14):LB-057. doi:10.1016/j.annonc.2020.08.691
10. Cai SX, Xu Q, Hu X, Jiang Y, Want G, Tian E. Abstract LB-057:1-Benzylquinazoline-2,4(1H,3H)-diones as potent PARP inhibitors. SAR of the quinazoline group and in vivo efficacy of clinical candidate IMP4297 [abstract]. In: Proceedings of the 107th Annual Meeting of the American Association for Cancer Research; 2016 April 16–20; New Orleans, LA. Philadelphia (PA): AACR. *Cancer Res*. 2016;76(14 suppl) Abstract no. LB-057. doi:10.1158/1538-7445.AM2016-LB-057
11. De Souza P, Gao B, Voskoboyonik M, et al. 574P Updated results of phase I study of senaparib (IMP4297) in Australian patients with advanced solid tumours. Poster presented at the European Society of Medical Oncology Virtual Congress; 2020 September 19–21. *Ann Oncol*. 2020;31(Suppl 4):S490. doi:10.1016/j.annonc.2020.08.688
12. Marcath LA, Coe TD, Hoylman EK, Redman BG, Hertz DL. Prevalence of drug-drug interactions in oncology patients enrolled on National Clinical Trials Network oncology clinical trials. *BMC Cancer*. 2018;18(1):1155. doi:10.1186/s12885-018-5076-0
13. Zanger UM, Schwab M. Cytochrome P450 enzymes in drug metabolism: regulation of gene expression, enzyme activities, and impact of genetic variation. *Pharmacol Ther*. 2013;138(1):103-141. doi:10.1016/j.pharmthera.2012.12.007
14. Sevrioukova IF, Poulos TL. Understanding the mechanism of cytochrome P450 3A4: recent advances and remaining problems. *Dalton Trans*. 2013;42(9):3116-3126. doi:10.1039/C2DT31833D
15. Molenaar-Kuijsten L, Van Balen DEM, Beijnen JH, Steeghs N, Huitema ADR. A review of CYP3A drug-drug interaction studies: practical guidelines for patients using targeted oral anticancer drugs. *Front Pharmacol*. 2021;12:670862. doi:10.3389/fphar.2021.670862
16. Klein K, Zanger UM. Pharmacogenomics of cytochrome P450 3A4: recent progress toward the "missing heritability" problem. *Front Genet*. 2013;4:12. doi:10.3389/fgene.2013.00012
17. Thummel KE. Gut instincts: CYP3A4 and intestinal drug metabolism. *J Clin Invest*. 2007;117(11):3173-3176. doi:10.1172/JCI34007
18. US Food and Drug Administration. Drug development and drug interactions: table of substrates, inhibitors and inducers. https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers#table 3–3. Accessed January 3, 2022.
19. Janssen Pharmaceuticals, SPORANOX® (itraconazole) capsules, for oral use. United States Food and Drug Administration. https://www.janssenlabels.com/package-insert/product-monograph/prescribing-information/SPORANOX-Capsules-pi.pdf. Accessed December 2022.
20. Sanofi-Aventis US LLC, RIFADIN® (rifampin) capsules, for oral use. United States Food and Drug Administration. https://products.sanofi.us/rifadin/rifadin.pdf May 2022.
21. US Food and Drug Administration. Guidance for industry. Bioavailability and bioequivalence studies for orally administrated drug products – general considerations. https://www.gmp-compliance.org/files/guidemgr/ucm154838.pdf. Accessed January 3, 2022.
22. Alexander SP, Fabbro D, Kelly E, et al. The concise guide to pharmacology 2021/22: enzymes. *Br J Pharmacol*. 2021;178(Suppl 1):S313-S411. doi:10.1111/bph.15542
23. US Department of Health and Human Services, National Institutes of Health, National Cancer Institute. Common Terminology Criteria for Adverse Events (CTCAE), Version 5.0. https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/ctcae_v5_quick_reference_5x7.pdf. Accessed November 5, 2021.
24. Clovis Oncology. RUBRACA® (rucaparib) [prescribing information]. https://clovisoncology.com/pdfs/RubracaUSPI.pdf. Accessed January 3, 2022.
25. Dirix L, Swaisland H, Verheul HM, et al. Effect of itraconazole and rifampin on the pharmacokinetics of olaparib in patients with advanced solid tumors: results of two phase I open-label studies. *Clin Ther*. 2016;38(10):2286-2299. doi:10.1016/j.clinthera.2016.08.010
26. GlaxoSmithKline. ZEJULA® (niraparib) [prescribing information]. https://gskpro.com/content/dam/global/hcpportal/en_US/Prescribing_Information/Zejula_Capsules/pdf/ZEJULA-CAPSULES-PI-PIL.PDF. Accessed January 3, 2022.
27. Pfizer Inc. TALZENNA® (talazoparib) [prescribing information]. https://labeling.pfizer.com/ShowLabeling.aspx?id=11046. Accessed January 3, 2022.

SUPPORTING INFORMATION

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

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