ORIGINAL RESEARCH ARTICLE

Pharmacokinetic Drug–Drug Interaction Studies Between Trilaciclib and Midazolam, Metformin, Rifampin, Itraconazole, and Topotecan in Healthy Volunteers and Patients with Extensive-Stage Small-Cell Lung Cancer

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Abstract

Background and Objective Trilaciclib is a cyclin-dependent kinase 4/6 inhibitor indicated to decrease the incidence of chemotherapy-induced myelosuppression in patients with extensive-stage small-cell lung cancer. Trilaciclib is a substrate and time-dependent inhibitor of cytochrome P450 3A4 and an inhibitor of multidrug and toxin extrusion 1, multidrug and toxin extrusion 2-K, organic cation transporter 1, and organic cation transporter 2. Here, we investigate the pharmacokinetic drug–drug interaction potential of trilaciclib.

Methods Two phase I studies were conducted as prospective, open-label, fixed-sequence drug–drug interaction studies in healthy subjects ($n = 57$, $n = 20$) to investigate potential interactions between intravenously administered trilaciclib (200 or 240 mg/m^2) and orally administered midazolam (5 mg), metformin (1000 mg), itraconazole (200 mg), and rifampin (600 mg). A population pharmacokinetic model was fit to phase Ib/IIa data in patients with extensive-stage small-cell lung cancer ($n = 114$) to assess the impact of trilaciclib dose and exposure (area under the plasma concentration–time curve) on topotecan clearance.

Results Coadministration with trilaciclib had minimal effects on the exposure (area under the plasma concentration–time curve from time 0 to infinity) of midazolam (geometric least-square mean ratio [GMR] vs midazolam alone 1.065; 90% confidence interval [CI] 0.984–1.154) but statistically significantly increased plasma exposure (GMR 1.654; 90% CI 1.472–1.858) and decreased renal clearance (GMR 0.633; 90% CI 0.572–0.701) of metformin. Coadministration of trilaciclib with rifampin or itraconazole decreased trilaciclib area under the plasma concentration–time curve from time 0 to infinity by 17.3% (GMR 0.827; 90% CI 0.785–0.871) and 14.0% (GMR 0.860; 0.820–0.902), respectively, vs trilaciclib alone. Population pharmacokinetic modeling showed no significant effect of trilaciclib on topotecan clearance.

Conclusions Overall, the drug–drug interaction and safety profiles of trilaciclib in these studies support its continued use in patients with extensive-stage small-cell lung cancer.

Clinical Trial Registration Study 106: EudraCT number: 2019-002303-18; Study 114: not applicable; Study 03: Clinicaltrials.org: NCT02514447; August 2015.

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Key Points

Drug–drug interaction studies showed no clinically meaningful differences in trilaciclib pharmacokinetics when used concomitantly with itraconazole (strong cytochrome P450 3A inhibitor) and rifampin (strong cytochrome P450 3A inducer), and no clinically meaningful differences in midazolam (cytochrome P450 3A substrate) pharmacokinetics when used concomitantly with trilaciclib.

The concomitant use of trilaciclib increased metformin (organic cation transporter 2, multidrug and toxin extrusion 1, and multidrug and toxin extrusion 2K substrate) exposure, and decreased renal clearance of metformin.

There were no clinically significant differences in topotecan (multidrug and toxin extrusion 1 and multidrug and toxin extrusion 2K substrate) pharmacokinetics when used concomitantly with trilaciclib.

1 Introduction

Trilaciclib is a first-in-class, intravenous (IV) cyclin-dependent kinase (CDK)4/6 inhibitor that is indicated to decrease the incidence of chemotherapy-induced myelo-suppression in adult patients when administered within 4 hours (h) prior to a platinum/etoposide-containing regimen or topotecan-containing regimen for extensive-stage small-cell lung cancer (ES-SCLC) [1]. Approval of trilaciclib was supported by data from three individual phase II trials in which trilaciclib was administered prior to standard chemotherapy in patients with ES-SCLC: Study G1T28-05 (NCT03041311) in patients with newly diagnosed ES-SCLC treated with etoposide plus carboplatin plus atezolizumab [2]; Study G1T28-02 (NCT02499770) in patients with newly diagnosed ES-SCLC treated with etoposide plus carboplatin [3]; and Study G1T28-03 (NCT02514447) in patients with ES-SCLC treated with second-line/third-line topotecan [4]. In each of these studies, administering trilaciclib prior to chemotherapy resulted in robust myeloprotection benefits across multiple hematopoietic lineages, without affecting the antitumor efficacy of chemotherapy [2–4]. Trilaciclib was well tolerated; adverse events (AEs) occurring more frequently with trilaciclib were fatigue, hypocalcemia, hypokalemia, hypophosphatemia, aspartate aminotransferase increase, headache, and pneumonia. Most AEs were grade 1 or 2 in intensity [1, 5].

Mechanistically, trilaciclib transiently arrests CDK4/6-dependent proliferating cells (e.g., hematopoietic stem and progenitor cells) in the G1 phase of the cell cycle during chemotherapy exposure, thus protecting them from chemotherapy-induced damage [6, 7]. Pharmacokinetic analysis indicates that the maximum concentration (C_{max}) of trilaciclib increases with dose proportionally, whereas total plasma exposure (area under the plasma concentration–time curve from time 0 to the time of last quantifiable concentration [AUC_{0-last}]) increases are slightly greater than proportional over a dose range of 200–700 mg/m^2 [1]. The recommended dose of trilaciclib is 240 mg/m^2, based on an integrated analysis of pharmacokinetic/pharmacodynamic, efficacy, and safety data in preclinical studies and phase Ib/IIa clinical studies in patients with ES-SCLC [8]. At this dose, the C_{max} of trilaciclib following a single dose is approximately 1500 ng/mL (~ 3 μM). There is no accumulation of trilaciclib following repeated dosing. The mean terminal half-life ($t_{1/2}$) is approximately 14 h, with clearance estimated to be 158 L/h [1], which is greater than the rate of hepatic blood flow in humans [9]. The unbound fraction for trilaciclib in plasma is approximately 30% (data on file, G1 Therapeutics). Trilaciclib undergoes extensive metabolism with less than 10% of the parent molecule recovered in the excreta, and the parent molecule is the predominant circulating compound following IV administration. Excretion occurs mainly via the fecal route with a small contribution of renal excretion [1].

Patients with cancer are typically older and often present with multiple comorbidities requiring concomitant medication [10–12]; therefore, it is important to evaluate the drug–drug interaction (DDI) potential of new treatments. Evaluation of potential DDIs in in vitro and clinical studies is also recommended by healthcare authorities worldwide, including the US Food and Drug Administration, European Medicines Agency, and Japanese Pharmaceuticals and Medical Devices Agency [13–15]. In non-clinical studies, trilaciclib was mainly metabolized by cytochrome P450 (CYP) 3A4 and two non-CYP enzymes: aldehyde oxidase and flavin-containing monooxygenase. No other enzymes contribute to more than 20% of the trilaciclib clearance (data on file, G1 Therapeutics). The optimal method for assessing clinical DDIs involving non-CYP drug-metabolizing enzymes is not well established. To date, there is only one reported aldehyde oxidase-mediated drug interaction [16], and flavin-containing monooxygenase is not readily inhibited or induced [17]. Therefore, clinical DDI assessment for aldehyde oxidase and flavin-containing monooxygenase was not warranted. Trilaciclib is also a substrate of the P-glycoprotein transporter (data on file, G1 Therapeutics). In addition, trilaciclib shows potent inhibition of multidrug and toxin extrusion (MATE) 1, MATE2-K, organic cation transporter (OCT) 1, and OCT2 with half maximal inhibitory concentrations of 0.175, 0.071, 0.604, and 0.152 μM, respectively (data on file,

G1 Therapeutics). Therefore, trilaciclib may cause clinically relevant DDIs mediated by these enzymes and transporters. Conversely, a DDI may also result from the concurrent administration of trilaciclib with a CYP3A4 inducer or inhibitor. Possible DDIs with midazolam (a CYP3A4 substrate [14]), metformin (a substrate of OCT1, OCT2, OCT3, MATE1, and MATE2-K [18]), rifampin (a CYP3A4 inducer [19]), and itraconazole (a strong CYP3A4 inhibitor [20]) were therefore evaluated in two separate phase I studies. The primary objectives were to evaluate the effect of multiple IV doses of trilaciclib on the single oral dose pharmacokinetics of midazolam and metformin, the effect of multiple oral doses of rifampin on the single-dose pharmacokinetics of IV trilaciclib, and the effect of multiple oral doses of itraconazole on the single-dose pharmacokinetics of trilaciclib. The potential for increasing topotecan (a MATE1 and MATE2-K substrate) exposure was also evaluated with clinical data in patients with ES-SCLC [4] using a population pharmacokinetic (popPK) approach.

2 Methods

2.1 Phase I Clinical DDI Studies

2.1.1 Study Designs, Participants, and Treatments

Two phase I studies were conducted as prospective, open-label, fixed-sequence DDI studies in healthy subjects (Study 106 [EudraCT Number: 2019-002303-18] and Study 114; Fig. 1). To be eligible, subjects were required to be healthy, aged 18–45 years (Study 114) or 18–55 years (Study 106), with a body mass index of 18–32 kg/m^2 (Electronic Supplementary Material [ESM]).

Study 106 consisted of two parts. Part A assessed the effect of multiple IV doses of trilaciclib on the pharmacokinetics of single oral doses of midazolam and metformin. Part B assessed the effect of multiple oral doses of rifampin on the pharmacokinetics of a single dose of IV administered trilaciclib (30-min infusion). In Part A, subjects received a single oral solution of midazolam 5 mg on day 1 and a single oral tablet of metformin 1000 mg on day 2, followed by washout. On days 4–9, subjects received once-daily 30-min IV infusions of trilaciclib 240 mg/m^2, with a single oral dose of midazolam 5 mg on day 8 and a single oral dose of metformin 1000 mg on day 9 (Fig. 1a). Trilaciclib was administered at the recommended dose (240 mg/m^2), and the concentrations of midazolam (5 mg), metformin (1000 mg), and rifampin (600 mg) were chosen based on the published literature [8, 21, 22]. Blood samples for the midazolam pharmacokinetic analysis were collected on days 1, 2, 8, and 9. Blood and urine samples for the metformin pharmacokinetic analysis were collected on days 2–4 and 9–11. In Part B, subjects received IV trilaciclib 240 mg/m^2 on day 1, followed by washout on days 2 and 3. They then received daily oral doses of rifampin 600 mg (capsule formulation) from days 4–13, with a second 30-min IV infusion of rilaciclib 240 mg/m^2 on day 11 (Fig. 1b). Blood samples for the trilaciclib pharmacokinetic analysis were collected on days 1–4 and 11–14. The blood/urine sampling scheme is presented in Fig. 1.

Study 114 assessed the effects of itraconazole on the single-dose pharmacokinetics of trilaciclib. Subjects received a 30-min IV infusion of trilaciclib 200 mg/m^2 on day 1, followed by a washout period on days 2 and 3. They then received daily oral doses (solution formulation) of itraconazole 200 mg on days 4–9, with a second 30-min IV infusion of trilaciclib 200 mg/m^2 on day 7, 2 h after itraconazole (Fig. 1c). As the victim drug, a trilaciclib dose of 200 mg/m^2 was chosen to ensure an adequate safety margin on the basis of linear pharmacokinetics between 200 and 240 mg/m^2 [1]. The itraconazole concentration (200 mg) was selected based on the published literature [23]. Blood samples for the trilaciclib pharmacokinetic analysis were collected on days 1–4 and 7–10 and for the itraconazole pharmacokinetic analysis on days 4–7. The blood sampling scheme is presented in Fig. 1.

The use of any concomitant medications/products (except paracetamol [up to 2 g/day]) was not permitted during either study without a rationale for exception or unless deemed necessary for the treatment of AEs. All treatments were administered to subjects in the morning after an overnight fast of at least 10 h following a light meal the previous evening.

The studies were conducted in accordance with the principles of the Declaration of Helsinki, the International Council for Harmonisation guideline for Good Clinical Practice, and national and local laws and regulations. The study protocols and informed consent documents were approved by the institutional review board or independent ethics committee at each participating site. All subjects provided written informed consent before the initiation of study procedures.

2.1.2 Pharmacokinetic and Statistical Analysis

Drug concentration measurements in plasma or urine were performed at PRA Bioanalytical Laboratory (now part of ICON plc., Dublin, Ireland) using validated liquid chromatography (LC) mass spectrometry/mass spectrometry methods (ESM). Method validation and sample analyses followed 2018 Food and Drug Administration bioanalytical guidance [24]. For trilaciclib, a 50-µL plasma sample was extracted by protein precipitation and analyzed by API Triple Quad 6500 (AB Sciex, Framingham, MA, USA) using a multiple reaction monitoring (MRM) scan (*m/z* 447.3→336.2). Chromatography separation was achieved
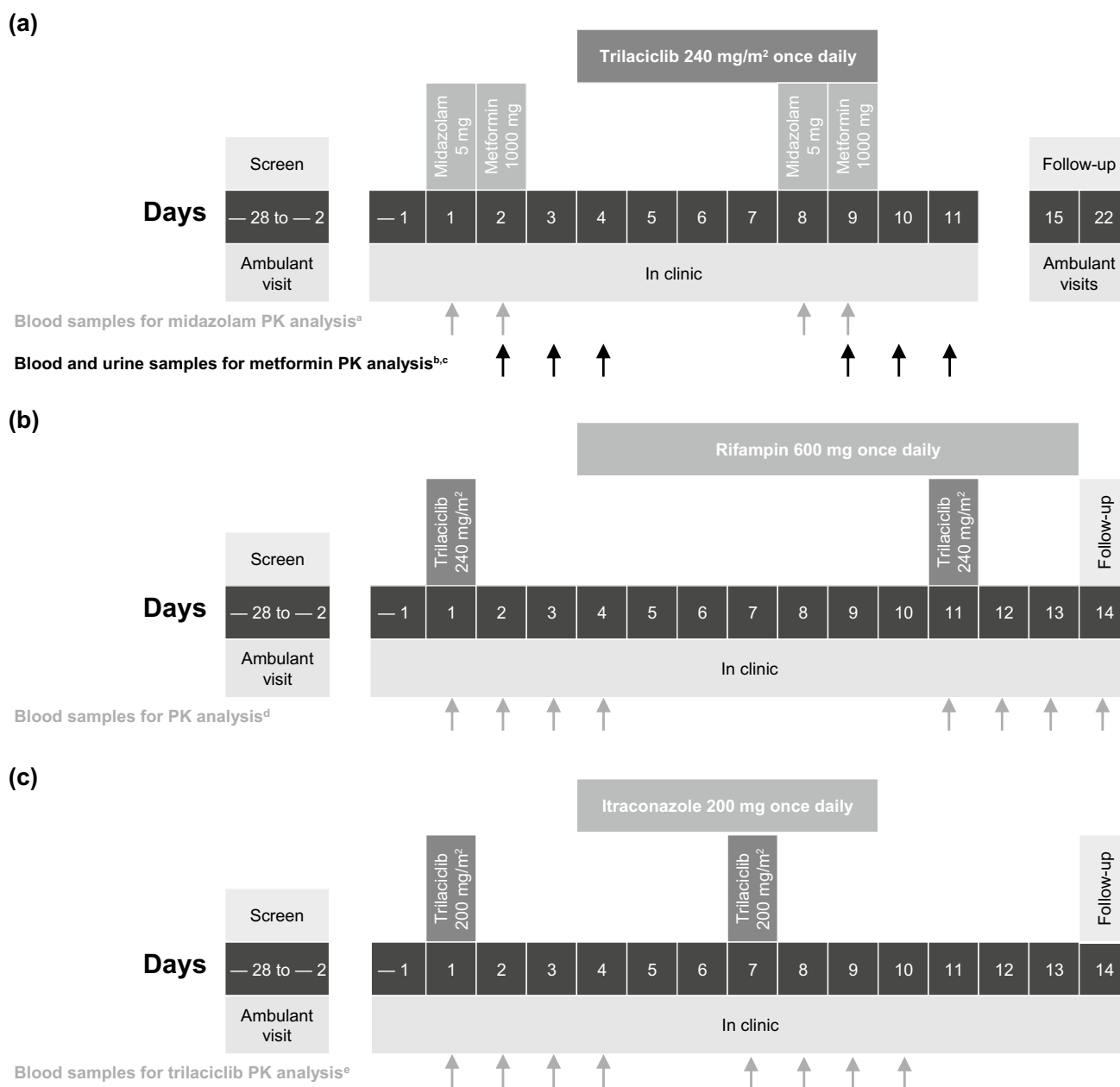
(a)

(b)

(c)

Fig. 1 Study designs of **a** Study 106 Part A, **b** Study 106 Part B, and **c** Study 114. [a]Blood sampling for the pharmacokinetics of midazolam in plasma at pre-dose and at 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 16, and 24 h post-midazolam dosing on days 1 and 8. [b]Blood sampling for the pharmacokinetics of metformin in plasma at pre-dose and at 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 10, 12, 24, 36, and 48 h post-metformin dosing on days 2 and 9. [c]Urine collection for the pharmacokinetics of metformin within 12 h prior to metformin dosing on days 2 and 9 and at collection intervals of 0–24 h and 24–48 h post-metformin dosing on days 2 and 9. [d]Blood sampling for the pharmacokinetics of trilaciclib in plasma at pre-dose and at 0.25, 0.42 (25 min), 0.5 (i.e., prior to the end of the trilaciclib infusion), 0.75, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 36, 48, and 72 h after the start of the trilaciclib infusion on days 1 and 11. [e]Blood sampling for the pharmacokinetics of trilaciclib in plasma at pre-dose (0 h) and at 0.25, 0.4, 0.5 (i.e., prior to the end of the trilaciclib infusion), 0.75, 1.0, 1.5 2, 3, 4, 6, 8, 12, 24, 36, 48, and 72 h after the start of the trilaciclib infusion on days 1 and 7. Blood samples of 2 mL (Study 106) or 6 mL (Study 114) were collected per analyte from each subject at each timepoint. The samples were taken via an indwelling intravenous catheter or by direct venipuncture into dipotassium-ethylenediaminetetraacetic acid-containing tubes. Blood samples were centrifuged to convert to plasma and stored at − 20 or − 70 °C until analysis (ESM). *PK* pharmacokinetic

using a Waters XBridge C18 column (Waters Corporation, Milford, MA, USA; 2.1 × 50 mm, 3.5-μm particles) with 0.1% ammonium hydroxide in water as mobile phase A and 50:50:0.1 acetonitrile:methanol:ammonium hydroxide v/v/v as mobile phase B, operating at a 0.500-mL/min flow rate under isocratic conditions. For itraconazole, a

50-μL plasma sample was extracted by liquid-liquid extraction and analyzed by API Triple Quad 5500 using MRM scan (*m/z* 705.3→392.3). Chromatography separation was achieved using a Waters Acquity UPLC BEH C18 column (50 × 2.1 mm, 1.7-μm particles) with 10 mM of ammonium formate with 1% formic acid as mobile phase A and 50:50:1 acetonitrile:methanol:formic acid v/v/v as mobile phase B, operating at a flow rate of 0.700-mL/min under isocratic conditions. For metformin, a 50-μL plasma sample was extracted by solid-phase extraction or a 25-μL urine sample was diluted prior to analysis. Extracted or diluted samples were analyzed by API Triple Quad 5500 using MRM scan (*m/z* 130.1→68.0). Chromatography separation was achieved using an Agilent Zorbax 300-SCX column (Agilent, Santa Clara, CA, USA; 3.0 × 50 mm, 5-μm particles) with 50 mM of ammonium formate (pH 2.5) as mobile phase A and acetonitrile as mobile phase B, operating at isocratic conditions with a flow rate of 1.00-mL/min. For midazolam, a 100-μL plasma sample was extracted by liquid-liquid extraction and analyzed by API Triple Quad 5500 using an MRM scan (*m/z* 326.1→291.0). Chromatography separation was achieved using a Waters Xbridge C18 column (2.1 × 50 mm, 3.5-μm particles) with 0.1% ammonium hydroxide in water as mobile phase A and methanol as mobile phase B, operating at a flow rate of 0.600-mL/min. For topotecan, a 100-μL plasma sample was extracted by solid-phase extraction and analyzed by API Triple Quad 6500 using an MRM scan (*m/z* 422.2→377.1). Chromatography separation was achieved using a Waters Acquity UPLC BEH C18 column (2.1 × 50 mm, 1.7-μm particles) with gradient elution, using 100:0.5 water:formic acid v/v as mobile phase A and 100:0.5 acetonitrile:formic acid v/v as mobile phase B, operating at a flow rate of 0.900-mL/min. Waters Acquity ultra-performance LC was used for all LC separations. Stable-labeled internal standards were used for all analytes (trilaciclib-d_3, itraconazole-d_9, metformin-d_6, midazolam-d_4, and topotecan-d_6).

Pharmacokinetic parameters were estimated using a non-compartmental analysis with WinNonlin® Version 8.1 (Certara, Princeton, NJ, USA). Calculated parameters included C_{max}, time to C_{max}, $AUC_{0–last}$ and area under the plasma concentration–time curve from time 0 to infinity ($AUC_{0–inf}$), $t_{1/2}$, total clearance, apparent total clearance, and apparent terminal volume of distribution. Area under the plasma concentration–time curve (AUC) was calculated using the linear-log trapezoidal approach. Statistical analyses were conducted using SAS® software (SAS Institute, Cary, NC, USA). Descriptive statistics were reported for pharmacokinetic concentrations and parameters. To investigate the effects of trilaciclib on the pharmacokinetics of midazolam and metformin and the effects of rifampin and itraconazole on trilaciclib pharmacokinetics, the natural log-transformed $AUC_{0–inf}$, $AUC_{0–last}$, and C_{max} of the respective compounds were assessed using a linear mixed-effects model, with treatment as a fixed effect and subject as a random effect. For metformin, the effect of trilaciclib was also assessed for renal clearance. Renal clearance was calculated by the amount of trilaciclib excreted in urine divided by the AUC [$CL_R = Ae_{urine,0–last}/AUC_{0–last}$]. Geometric least-square mean ratios (GMRs) and corresponding 90% confidence intervals (CIs) were estimated by exponentiating the mean differences in the logarithm. In all studies, 90% CIs for the GMRs were used to evaluate the effects of perpetrator drugs on victim drug C_{max} and AUCs. The default no-effect boundary of 0.8–1.25 was used as the criteria to judge if the DDI magnitude was statistically significant. If the 90% CIs for GMR were completely within the 0.8–1.25 range, this was concluded as a negative DDI. If the 90% CI for GMR was outside the default no effect boundary, the implication for recommendations on dose adjustment was based on its clinical significance.

A bioequivalence approach (i.e., two one-sided tests at two-sided alpha of 10%) was used to calculate the sample size for Studies 106 and 114. Assumptions for within-subject variance were obtained from previous pharmacokinetic studies for trilaciclib or literature values for other probe substrates. The calculation assumed that point estimation for GMRs between the test (perpetrator drug and victim drug) and reference (victim drug alone) for C_{max} and AUC were equal to 1. The sample size was selected to ensure 80% power to demonstrate GMRs between the test and reference of between 0.8 and 1.25 for both C_{max} and AUC. Additional subjects were included to account for potential dropout.

2.1.3 Safety Assessments

Safety assessments included evaluation of AEs, clinical laboratory parameters, vital signs, 12-lead electrocardiograms, and physical examinations. Adverse events were monitored from admission (day 1 [Study 106]) or first dose administration (day 1 [Study 114]) through to the last follow-up visit on day 14 (Study 106, Part B and Study 114) or day 22 (Study 106, Part A). Treatment-emergent AEs (TEAEs) were defined as AEs that occurred after the first dose of any study drug. Adverse events were classified using Medical Dictionary for Regulatory Activities Version 22.0 and graded using the Common Terminology Criteria for Adverse Events Version 5.

2.2 PopPK Analysis of Topotecan in Study 03

2.2.1 Study Design, Participants, and Treatments

Study G1T28-03 (ClinicalTrials.gov Identifier: NCT02514447) was a multicenter phase Ib/IIa study of trilaciclib given prior to the administration of topotecan in

patients with previously treated ES-SCLC. Full patient eligibility criteria have been described previously [4]. The study comprised two parts: a limited, open-label, dose-finding portion with a starting dose of IV trilaciclib 200–280 mg/m^2 once daily prior to topotecan 0.75–1.5 mg/m^2 on days 1–5 of each 21-day cycle and a randomized, double-blind, placebo-controlled portion in which patients were randomized (2:1) to receive IV trilaciclib 240 mg/m^2 or placebo prior to topotecan 1.5 mg/m^2. Blood samples for the pharmacokinetic analysis of trilaciclib and topotecan were collected in a rich sampling approach that allowed for the estimation of trilaciclib AUC using a non-compartmental approach. For Part 1, samples were collected in cycle 1 on days 1 and 4 at pre-dose and at 0.5, 1, 1.5, 2, 2.5, 3, 4.5, 6.5, 8.5 (optional), and 24.5 h post-dose. For Part 2, samples were collected in cycle 1 on days 1 and 4 at pre-dose and at 0.5, 1, 3–4, and 5.5–6.5 h post-dose. For both parts, 5-mL blood samples were collected per analyte from each subject at each time-point. Samples were taken via an indwelling IV catheter or by direct venipuncture into dipotassium-ethylenediaminetetraacetic acid-containing tubes. Blood samples were processed to plasma and stored at − 70 °C until analysis. Topotecan plasma concentrations were determined at PRA Bioanalytical Laboratory using validated ultra-performance LC with tandem mass spectrometry detection (ESM).

2.2.2 PopPK Model for Topotecan

Population pharmacokinetic analyses were performed using non-linear mixed effects modeling (NONMEM® Version 7.3; ICON plc., Dublin, Ireland) using the first-order conditional estimation with interaction method. Missing concentration values were not included in the analysis dataset. If topotecan and trilaciclib dose amounts were missing, the dose was calculated as [baseline body surface area] × [planned mg/m^2 dose] × [percent of dose infused/100]. Model development procedures began with the evaluation of a structural model that included a base model, statistical model, and residual model. Based on visual inspection of the concentration data showing a multi-exponential decline of drug concentrations, development of the base model began with the fitting of structural pharmacokinetic models with two and three compartments. As trilaciclib is administered by an IV infusion, no absorption compartments were included in the structural model. Interindividual variability was included initially using an exponential model on all parameters. Residual unexplained variability was initially modeled with a proportional error component. The number of random effects describing interindividual variability and alternative residual error models (i.e., proportional vs additive and proportional) was evaluated with an iterative process. Model evaluation and selection were based on standard

criteria such as difference in objective function value (OFV; − 2 × log-likelihood) and by examining pertinent graphical representations of goodness of fit (e.g., fitted and observed concentration vs time, weighted residuals vs time). The quality of fit of the base model was evaluated using standard graphical representations of goodness of fit as follows: observed data versus population predicted data and individual predicted data; conditional weighted residuals (CWRES) versus predicted data, time, and time after dose; and quantiles-quantiles plot of CWRES (Q–Q plot). In addition, estimation of individual random effect (ETA) shrinkage was evaluated for diagnostic purposes.

Following structural model development and refinement, prespecified covariate hypotheses were evaluated graphically, followed by formal testing with forward addition and backward elimination. During forward addition, covariates were added to fixed effects, one covariate at a time. A minimum decrease in the OFV of at least 3.841 ($p \leq 0.05$) and/or improvement in diagnostic plots was required for retention for forward addition steps with one added parameter. Prespecified covariate-parameter relationships were selected based on known or physiologically rational factors that could affect pharmacokinetics but were tested only if an effect was suggested by plots, except for covariates included in the preliminary model (weight and creatinine clearance), which were formally tested for inclusion in the final model. Covariates examined included body size (weight, body mass index, or body surface area), sex, race, creatinine clearance, age, aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, bilirubin, albumin, hepatic function class (National Cancer Institute classification), renal function class (National Cancer Institute classification), H$_2$ antagonists, ondansetron or other 5HT$_3$ antagonists, and trilaciclib dose, AUC, and clearance. With the presence of collinear covariates (e.g., age and renal function), each covariate was added independently and only the most plausible covariate (based on goodness of fit and physiology) was retained in the model. Following the forward addition steps, a backward elimination procedure was implemented during which each covariate was removed from the full model univariately. A minimum increase of 6.635 in the OFV ($p \leq 0.01$) was required for the retention of covariates in all backward elimination steps with one eliminated parameter. The decision to include a covariate was not based solely on the change in the OFV: goodness-of-fit plots, the precision of estimates, and the magnitude of interindividual and residual variability were all considered, with the goal of describing a conservative model with adequate precision for simulation. The final model was evaluated using standard goodness-of-fit plots and visual predictive checks, and precision of the model parameter estimates was assessed by non-parametric bootstrapping ($n = 1000$ replicates).

3 Results

3.1 Phase I Clinical DDI Studies

3.1.1 Subjects

In Study 106, 33 subjects were enrolled in Part A and 24 in Part B. Ten subjects in Part A discontinued because of AEs (8/8 at Site 1 and 2/25 at Site 2), and 47 subjects completed the study per protocol. In Study 114, 20 subjects enrolled and completed the study per protocol. Demographic and baseline characteristics are summarized in Table 1.

3.1.2 Impact of Trilaciclib on the Pharmacokinetic Profiles of Midazolam and Metformin: Study 106

Geometric mean plasma concentration–time profiles and pharmacokinetic parameters for midazolam and metformin when administered with or without trilaciclib (Part A) are shown in Fig. 2a, b and Table 2. Geometric mean AUCs of midazolam were 4.0% ($AUC_{0–last}$) and 4.6% ($AUC_{0–inf}$) higher after coadministration with trilaciclib than after midazolam alone (GMRs 1.060 [90% CI 0.980–1.147] for $AUC_{0–last}$ and 1.065 [90% CI 0.984–1.154] for $AUC_{0–inf}$), indicating no significant impact of trilaciclib on exposure to midazolam. The terminal $t_{1/2}$ was roughly the same with and without trilaciclib, indicating that the elimination rate of midazolam was unchanged. For C_{max}, the GMR CI was not fully within the default no-effect CI boundary of 0.8–1.25 (GMR 0.834; 90% CI 0.726–0.958); hence, the absence of an interaction could not be concluded for this parameter.

Geometric mean C_{max} of metformin was 79.8% higher after coadministration with trilaciclib than after metformin alone (GMR 1.811; 90% CI 1.574–2.083). Geometric mean AUCs of metformin were 66.0% ($AUC_{0–last}$) and 64.6% ($AUC_{0–inf}$) higher after coadministration with trilaciclib than after metformin alone (GMR 1.669 [90% CI 1.482–1.879] for $AUC_{0–last}$ and 1.654 [90% CI 1.472–1.858] for $AUC_{0–inf}$). Geometric mean renal clearance of metformin was decreased by 36.7% when coadministered with trilaciclib (GMR 0.633; 90% CI 0.572–0.701). The 90% CIs of the ratios were fully outside the default no-effect boundaries of 0.8–1.25, indicating that trilaciclib significantly increased plasma exposure to metformin and significantly decreased renal clearance of metformin.

3.1.3 Impact of Rifampin on the Pharmacokinetic Profile of Trilaciclib: Study 106

After coadministration of trilaciclib and repeated rifampin dosing, the terminal $t_{1/2}$ was roughly the same with and without rifampin, indicating that the elimination rate of trilaciclib was unchanged. The geometric mean C_{max} of trilaciclib was reduced by 19.9% compared with that observed with trilaciclib alone (GMR 0.801; 90% CI 0.697–0.920; Fig. 2c and Table 3). Geometric mean AUCs of trilaciclib decreased by 17.3% ($AUC_{0–last}$ GMR 0.827 [90% CI 0.785–0.872]; $AUC_{0–inf}$ GMR 0.827 [90% CI 0.785–0.871]) when coadministered with rifampin. The 90% CIs of the ratios were not fully within the default no-effect range of 0.80–1.25; therefore, an absence of interaction could not be concluded.

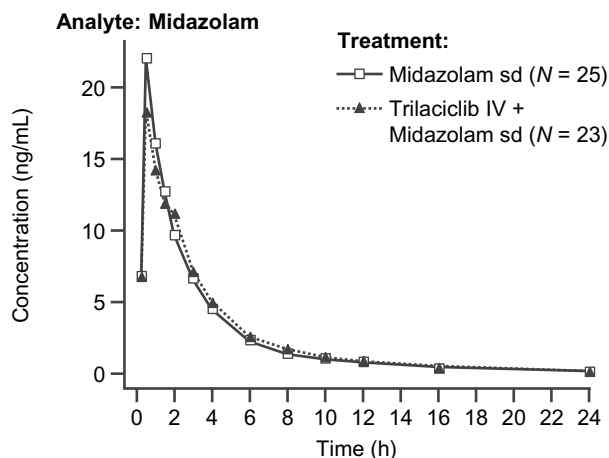### 3.1.4 Impact of Itraconazole on the Pharmacokinetic Profile of Trilaciclib: Study 114

After coadministration of trilaciclib with itraconazole, the terminal $t_{1/2}$ was roughly the same with and without itraconazole, indicating that the elimination rate of trilaciclib was unchanged. The geometric mean C_{max}, $AUC_{0–last}$, and

Table 1 Demographic and baseline characteristics of subjects included in the two phase I drug–drug interaction studies (safety population)
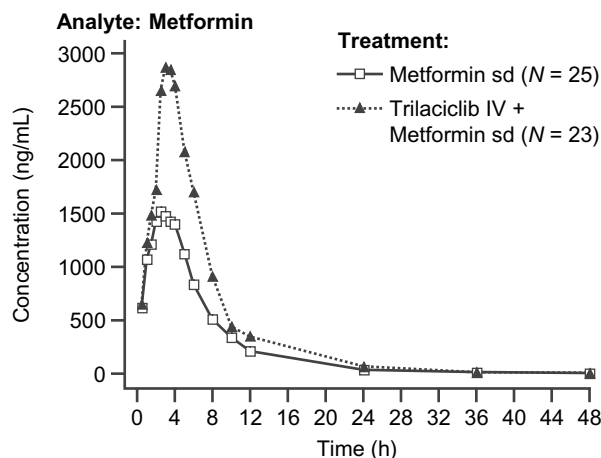
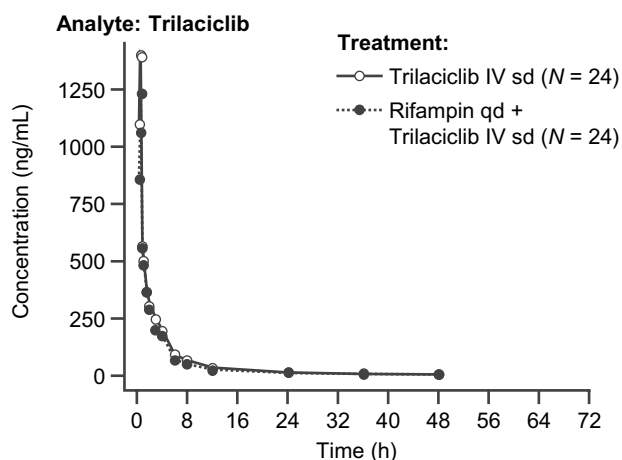| Characteristic	Study 106		Study 114
	Part A ($N = 33$)	Part B ($N = 24$)	($N = 20$)
Age, years, median (range)	32.0 (19–55)	31.0 (19–49)	33.0 (19–44)
BMI, kg/m^2, mean (SD)	26.20 (3.71)	24.92 (3.34)	26.50 (3.41)
Female sex, n (%)	2 (6.1)	1 (4.2)	3 (15.0)
Race, n (%)			
American Indian or Alaska Native	2 (6.1)	1 (4.2)	0 (0)
Asian	1 (3.0)	2 (8.3)	0 (0)
Black or African American	1 (3.0)	5 (20.8)	9 (45.0)
White	28 (84.8)	16 (66.7)	11 (55.0)
Asian + Black or African American	1 (3.0)	0 (0)	0 (0)
Hispanic or Latino ethnicity, n (%)	3 (9.1)	9 (37.5)	2 (10.0)

BMI body mass index, *SD* standard deviation

(a) Study 106 Part A

Analyte: Midazolam

(b) Study 106 Part A

Analyte: Metformin

(c) Study 106 Part B

Analyte: Trilaciclib

(d) Study 114
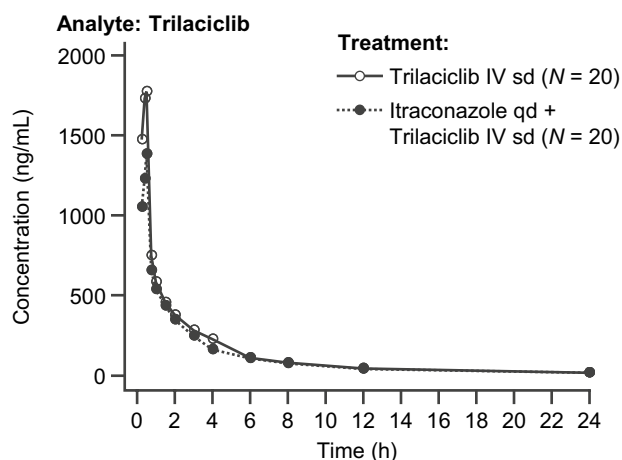
Analyte: Trilaciclib

Fig. 2 Geometric mean plasma concentration–time profiles of **a** midazolam and **b** metformin with and without trilaciclib; **c** trilaciclib with and without rifampin; and **d** trilaciclib with and without itraconazole. Linear scale. *h* hours, *IV* intravenous, *qd* once daily, *sd* single dose

AUC_{0-inf} values of trilaciclib decreased by 28.0, 13.3, and 13.6%, respectively (Fig. 2d; Table 4). Geometric least-square mean ratios and 90% CIs were 0.711 (0.617–0.820) for C_{max}, 0.856 (0.817–0.896) for AUC_{0-last}, and 0.860 (0.820–0.902) for AUC_{0-inf}. The 90% CIs of the GMRs for AUC_{0-last} and AUC_{0-inf} were within the default no-effect range of 0.80–1.25, whereas the lower bound for C_{max} was lower. Therefore, there was no evidence that itraconazole increases trilaciclib exposure.

3.1.5 Safety

Adverse events across the two phase I DDI studies are shown in Table 5. In Study 106, all subjects reported at least one TEAE. The initial eight subjects were discontinued because of phlebitis in the arm related to trilaciclib administration (12 events in total). Drug administration modifications

were subsequently implemented for the next 25 subjects to mitigate the risk of phlebitis. For the 25 subjects enrolled after the adjustment of drug administration, there were 79 TEAEs of infusion/injection-related reactions (e.g., pain, erythema, and swelling) reported by 23 (92%) subjects, and only seven TEAEs of thrombophlebitis reported by six (24%) subjects; no subjects withdrew because of infusion/injection-related reactions. There were no serious TEAEs. However, six subjects experienced Grade 3 ($n = 5$) or Grade 4 ($n = 1$) TEAEs of neutropenia related to trilaciclib; all resolved without intervention. Two TEAEs (influenza unrelated to trilaciclib and asymptomatic Grade 1 ventricular tachycardia possibly related to trilaciclib) in two subjects led to early study drug withdrawal. In Part B, there were 16 infusion/injection-related reaction TEAEs reported by 12 subjects and one thrombophlebitis TEAE. No TEAEs led to withdrawal, and all TEAEs were mild or moderate in

Table 2 Summary of pharmacokinetic parameters for midazolam (in plasma) and metformin (in plasma and urine) when administered alone and in combination with trilaciclib

	Geometric mean (CV%)							
	C_{max} (ng/mL)	t_{max}[a] (h)	AUC_{0-last} (h·ng/mL)	AUC_{0-inf} (h·ng/mL)	AUC_{0-48} (h·ng/mL)	$t_{1/2}$ (h)	CL/F (L/h)	V_z/F (L)
Midazolam alone (N = 25)	24.4 (35.3)	0.50 (0.25–1.50)	62.1 (34.3)	64.6 (34.2)	–	5.68 (27.0)	77.4 (34.2)	635 (40.1)
Trilaciclib + midazolam (N = 23)	20.3 (37.6)	0.50 (0.25–2.00)	64.6 (29.2)	67.6 (30.4)	–	6.17 (37.5)	74.0 (30.4)	658 (38.6)
GMR (90% CI)	0.834 (0.726–0.958)	–	1.060 (0.980–1.147)	1.065 (0.984–1.154)	–	–	–	–
Metformin alone (N = 25)	1647 (34.2)	2.50 (1.50–5.00)	11,728 (32.2)	11,939 (31.8)	11,753 (32.0)	9.66 (45.9)	83.8 (31.8)	1167 (61.2)
Trilaciclib and metformin (N = 23)	2962 (32.7)	3.00 (2.50–4.00)	19,470 (30.8)	19,650 (30.8)	19,492 (30.7)	7.58 (37.0)	50.9 (30.8)	556 (47.8)
GMR (90% CI)	1.811 (1.574–2.083)	–	1.669 (1.482–1.879)	1.654 (1.472–1.858)	–	–	–	–

	Ae (mg)	Fe (%)	CL_R (L/h)
Metformin alone (N = 25)	342 (25.1)	34.2 (25.1)	28.6 (30.0)
Trilaciclib + metformin (N = 23)	356 (31.9)	35.6 (31.9)	18.1 (25.0)
GMR (90% CI)	–	–	0.633 (0.572–0.701)

Ae total amount of drug excreted in urine, AUC_{0-48} area under the plasma concentration–time curve from time 0 to time 48 h post-dose, AUC_{0-inf} area under the plasma concentration–time curve from time 0 to infinity, AUC_{0-last} area under the plasma concentration–time curve from time 0 to the time of last quantifiable concentration, *CI* confidence interval, CL_R renal clearance, *CL/F* apparent oral clearance, calculated as dose/AUC_{0-inf}, C_{max} maximum observed plasma concentration, *CV* coefficient of variation, *Fe* percentage of drug excreted in urine, *GMR* geometric least-squares mean ratio, $t_{1/2}$ terminal phase half-life, t_{max} time to attain maximum observed plasma concentration, *Vz/F* apparent volume of distribution at terminal phase

[a]Median and range are provided for t_{max}

Table 3 Summary of pharmacokinetic parameters for trilaciclib in plasma when administered alone and in combination with rifampin

	Geometric mean (CV%)					
	C_{max} (ng/mL)	t_{max}[a] (h)	AUC_{0-last} (h·ng/mL)	AUC_{0-inf} (h·ng/mL)	$t_{1/2}$ (h)	CL (L/h)
Trilaciclib alone (N = 24)	1603 (53.2)	0.42 (0.25–0.50)	2672 (20.6)	2698 (20.5)	10.1 (17.5)	175 (21.7)
Trilaciclib + rifampin (N = 24)	1284 (45.9)	0.50 (0.25–0.50)	2210 (20.1)	2231 (20.0)	9.35 (17.4)	211 (20.6)
GMR (90% CI)	0.801 (0.697–0.920)	–	0.827 (0.785–0.872)	0.827 (0.785–0.871)	–	–

AUC_{0-inf} area under the plasma concentration–time curve from time 0 to infinity, AUC_{0-last} area under the plasma concentration–time curve from time 0 to the time of last quantifiable concentration, *CI* confidence interval, *CL* total plasma clearance, C_{max} maximum observed plasma concentration, *CV* coefficient of variation, *GMR* geometric least-squares mean ratio, $t_{1/2}$ terminal phase half-life, t_{max} time to attain maximum observed plasma concentration

[a]Median and range are provided for t_{max}

severity. All TEAEs in Parts A and B were fully resolved or were resolving by the end of the study.

In Study 114, ten subjects (50%) reported at least one TEAE, including one subject who experienced a moderate AE of headache. There were no serious TEAEs, and no subjects discontinued treatment because of AEs. One subject had a mild TEAE of alopecia with an unknown outcome at the end of the study; all other AEs resolved without sequela by the end of the study.

Table 4 Summary of pharmacokinetic parameters for trilaciclib in plasma when administered alone and in combination with itraconazole

	Geometric mean (CV%)					
	C_{max} (ng/mL)	t_{max}[a] (h)	$AUC_{0–last}$ (h·ng/mL)	$AUC_{0–inf}$ (h·ng/mL)	$t_{1/2}$ (h)	CL (L/h)
Trilaciclib alone ($N = 18$)	1769.8 (43.9)[b]	0.40 (0.25–0.50)[b]	3071.9 (16.3)[b]	3115.0 (16.4)	9.115 (13.2)	127.3 (18.4)
Trilaciclib + itraconazole ($N = 17$)	1274.8 (48.7)	0.48 (0.40–0.48)	2664.4 (20.2)	2691.5 (20.0)	9.070 (16.0)	147.2 (23.0)
GMR (90% CI)	0.711 (0.617–0.820)	–	0.856 (0.817–0.896)	0.860 (0.820–0.902)	–	–

$AUC_{0–inf,}$ area under the plasma concentration–time curve from time 0 to infinity, $AUC_{0–last}$ area under the plasma concentration–time curve from time 0 to the time of last quantifiable concentration, *CI* confidence interval, *CL* total plasma clearance, C_{max} maximum observed plasma concentration, *CV* coefficient of variation, *GMR* geometric least-squares mean ratio, $t_{1/2}$ terminal phase half-life, t_{max} time to attain maximum observed plasma concentration

[a]Median and range are provided for t_{max}

[b]$N = 19$

Table 5 Adverse events reported in the two phase I drug–drug interaction studies

	Study 106		Study 144
	Part A ($N = 33$)	Part B ($N = 24$)	($N = 20$)
Any TEAE, *n* (%)	33 (100)	24 (100)	10 (50.0)
TEAEs related to individual study drugs, *n* (%)			
Trilaciclib	33 (100)	20 (83.3)	9 (45.0)
Metformin	7 (21.2)	–	–
Midazolam	16 (48.5)	–	–
Rifampin	–	19 (79.2)	–
Itraconazole	–	–	2 (10.0)
TEAEs by severity, *n* (%)			
Grade 1	33 (100)	23 (95.8)	9 (45.0)
Grade 2	25 (75.8)	5 (20.8)	1 (5.0)
Grade 3	5 (15.2)	0	0
Grade 4	1 (3.0)	0	0
Serious TEAEs, *n* (%)	0	0	0
TEAEs leading to discontinuation, *n* (%)	10 (30.3)	0	0
Most frequently reported TEAEs by preferred term (≥ 3 subjects in any study/part)			
Injection-/infusion-related reaction	27 (81.8)	12 (50.0)	1 (5.0)
Headache	25 (75.8)	16 (66.7)	8 (40.0)
Neutropenia	17 (51.5)	1 (4.2)	0
Nausea	9 (27.3)	4 (16.7)	2 (10.0)
Infusion-site thrombosis	8 (24.2)	0	0
Fatigue	7 (21.1)	0	0
Somnolence	6 (18.2)	1 (4.2)	0
Infusion-site phlebitis	6 (18.2)	1 (4.2)	0
Dizziness	4 (12.1)	2 (8.3)	0
Diarrhea	3 (9.1)	0	1 (5.0)
Hyperhidrosis	3 (9.1)	0	0
Chromaturia	0	19 (79.2)	0

TEAE treatment-emergent adverse event

3.1.6 PopPK Analysis of Topotecan in Study 03

A total of 114 patients were included in the final popPK analysis (1007 total concentrations from 31 patients in Part 1 and 83 in Part 2). Ten concentration data values (~ 1%) were missing and were not replaced. Among 114 patients, 89 patients received trilaciclib (200−280 mg/m^2) prior to topotecan (0.75−1.5 mg/m^2), and 25 patients received topotecan alone (1.5 mg/m^2). Baseline characteristics are summarized in the ESM. The final topotecan popPK model was a three-compartment model with a weight effect on central volume of distribution and a creatinine clearance effect on topotecan clearance. The model parameters, goodness-of-fit plots and visual predictive checks are shown in the ESM. The effect of trilaciclib exposure on topotecan pharmacokinetics was assessed by examining the plots of CWRES [25] vs trilaciclib dose or AUC. As shown in the ESM, trilaciclib dose and AUC did not show any correlation with CWRES, indicating that trilaciclib does not impact topotecan pharmacokinetics.

4 Discussion

Investigation of potential CYP enzyme-mediated and transporter-mediated DDIs is a standard part of drug evaluations. Like trilaciclib, oral CDK4/6 inhibitors (palbociclib, ribociclib, and abemaciclib) are also metabolized by CYP3A and are time-dependent inhibitors of this enzyme [26]. Drug–drug interaction studies suggest that strong CYP3A inducers decrease plasma exposure to oral CDK4/6 inhibitors, leading to potential therapeutic failure, whereas strong CYP3A inhibitors increase their exposure, potentially resulting in increased toxicity [26]. Consequently, their labels recommend avoiding concomitant use with strong CYP3A4 inducers or inhibitors [27–29]. By contrast, in our study, coadministration of trilaciclib with the strong CYP3A inhibitor itraconazole was not considered to have clinically meaningful effects on the exposure of trilaciclib, with the 90% CIs of the GMRs for AUC falling within the default no-effect range. The reason why the lower bound for C_{max} was below 80% is not clear. With a short duration of IV infusion (i.e., 30 min), C_{max} is more influenced by volume of distribution than by systemic clearance. Trilaciclib is a substrate of P-glycoprotein, and itraconazole is a P-glycoprotein inhibitor, which may allow better penetration into tissues leading to lower C_{max}. The effect on C_{max} could also be related to the observed variability in C_{max}. For IV infusion, the C_{max} occurs exactly at the end of infusion. Immediately after C_{max}, trilaciclib concentration dropped rapidly with a $t_{1/2}$ of 15 min in the distribution phase. Therefore, the true C_{max} may not be captured owing to the challenge of determining the exact time for blood sampling at the end of an infusion.

Most importantly, however, there was no evidence that itraconazole will increase the overall exposure of trilaciclib. There was also no clinically meaningful decrease in plasma exposure to trilaciclib when coadministered with repeated oral doses of the strong CYP3A4 inducer rifampin, although the absence of an interaction could not be concluded. Of note, in addition to 240 mg/m^2, the efficacy and safety of trilaciclib in patients with ES-SCLC have also been evaluated using doses of 200 and 280 mg/m^2 (approximately 20% lower and higher than the recommended dose, respectively). Although dose response data slightly favored 240 mg/m^2 over 200 mg/m^2 in terms of laboratory values, the exposure–response analysis indicated that, across the exposure range for doses of 200–280 mg/m^2, there was a relatively flat exposure–response relationship (data on file, G1 Therapeutics). Based on these findings, a decrease of 17% in trilaciclib AUC when coadministered with rifampin is not expected to impact its clinical efficacy. Overall, concurrent administration with CYP3A inhibitors or inducers does not appear to have a clinically meaningful impact on trilaciclib exposure.

In Study 106, trilaciclib was given for 6 days to assess the time-dependent effect on CYP3A4. For drugs with time-dependent inhibition propensities, a delay in reaching the maximum inhibitory effect can occur after the pharmacokinetics reaches steady state. The study design was selected because the approved regimens for trilaciclib in patients with ES-SCLC are repeated administration for either 3 or 5 days [1]. A longer duration of trilaciclib administration will therefore be clinically irrelevant. There was no clinically meaningful inhibition of CYP3A4 by trilaciclib when midazolam was used as an index substrate. Total exposure to midazolam did not change significantly upon trilaciclib infusion, but C_{max} decreased by 16.6% after multiple IV doses of trilaciclib without obvious mechanistic explanation. However, midazolam is absorbed rapidly, meaning that the C_{max} is difficult to capture accurately.

Owing to safety concerns (i.e., neutropenia) in healthy volunteers following repeated dosing, trilaciclib dosing did not extend beyond 6 days during the DDI assessment with metformin, fully covering the pharmacokinetic sampling duration. Metformin AUC$_{0–24}$ represents approximately 95% of the AUC$_{0–inf}$ [30]. Therefore, the study design would not impact the assessment of the interaction between metformin and trilaciclib. We identified a statistically significant increase in plasma exposure to metformin (an OCT1, OCT2, OCT3, MATE1, and MATE2-K substrate [18]) when coadministered with repeated rilaciclib dosing, and an impact on the urinary excretion of a single oral dose of metformin. Metformin is not metabolized and is excreted unchanged in the urine [31]. Although plasma exposure increased, the total amount of metformin excreted in urine was not affected, indicating that the exposure increase was not due to a change

of bioavailability of metformin but was related to a decrease in clearance. If approximately 25% of the renal clearance of metformin is via glomerular filtration and 75% is through active secretion [32], the observed 36.7% decrease in overall renal clearance is expected to translate into an approximate 50% decrease of active secretion of metformin. This is likely caused by strong inhibition of multiple renal transporters: OCT1, OCT2, MATE1, and MATE2-K by trilaciclib [1] because the transport of metformin from the circulation into the renal epithelia is mediated by OCT2, with renal excretion mediated primarily by MATE1 and MATE2-K, and OCT1 involved in reabsorption in kidney tubules [33]. As trilaciclib showed strong inhibition of all four transporters (OCT1, OCT2, MATE1, and MATE2-K) in vitro, coadministration with metformin could represent a scenario where multiple transporters are inhibited by trilaciclib. However, the increase in metformin exposure is expected to be short-lived given the short half-life and intermittent dosing of trilaciclib (once daily for 3 or 5 days with long dosing holidays). In addition, the effect of trilaciclib on metformin (36.7% decrease in overall renal clearance) is similar to the effect of mild-to-moderate impaired renal function on metformin, for which no dose adjustment is recommended [34]. Therefore, it has been determined that trilaciclib dose modification for metformin is not warranted [1, 35].

Preliminary model development for the popPK analysis from Study G1T28-03 was initiated by fitting two-compartment structural models to the topotecan data, as reported in the literature [36]. A systematic trend in the CWRES vs time after dose plot was observed with such model fitting. However, this trend was eliminated by fitting a three-compartment model. The pharmacokinetics of topotecan was well described by a three-compartment model with a body weight effect on the central volume of distribution and a creatinine clearance effect on topotecan clearance. The final popPK model identified no significant effect of trilaciclib dose or AUC on topotecan clearance. This suggests that no topotecan dosage adjustments are necessary with coadministration of trilaciclib over the range of baseline characteristics observed in the study. However, it is worth noting that the evaluation of the DDI between trilaciclib and topotecan was conducted retrospectively. Therefore, the timing of the drug administrations was not designed to maximize the interaction potential (i.e., to maximize the overlap of exposure between trilaciclib and topotecan). The trilaciclib label recommends that trilaciclib is administered as a 30-min IV infusion within 4 h prior to the start of chemotherapy [1] and, as mentioned above, trilaciclib concentrations drop rapidly after the end of 30-min infusion (i.e., a rapid distribution phase). Therefore, when topotecan reaches its peak concentration, the circulating trilaciclib concentration is expected to be relatively low, which may explain the low drug interaction potential with topotecan.

Intravenous infusion of trilaciclib, administered alone or when coadministered with midazolam, metformin, rifampin, or itraconazole, was generally well tolerated. Almost all AEs were resolved or resolving by the end of the studies. The observed infusion/injection-related reactions are very common for IV infusion drugs. Half of the subjects experienced neutropenia following repeated dosing in Study 106, although this quickly resolved without treatment. Occurrence of neutropenia in the absence of concurrent myelotoxic chemotherapy with trilaciclib was likely owing to near long-term delivery and was expected in this population. Indeed, neutropenia has been observed as one of the most common Grade 3/4 AEs in clinical trials of oral CDK4/6 inhibitors, which are dosed long term for the treatment of breast cancer [37]. CDK4/6 inhibitor-associated neutropenia is rapidly reversible because proliferation of hematopoietic and progenitor stem cells resumes following dose reduction or interruption [6, 38]. By contrast, chemotherapy-associated neutropenia arises through apoptotic cell death [39]. Of note, trilaciclib differs from approved oral CDK4/6 inhibitors in its shorter half-life, method of administration, dosing schedule, and intended use with chemotherapy such that transient arrest with trilaciclib prevents rather than increases the incidence of severe neutropenia when administered according to the US prescribing information [1, 40].

Collectively, these studies indicate that, when administered at the recommended dosage, trilaciclib has few inhibitory or induction-related drug interactions, demonstrating a low potential for clinically relevant DDIs. The increased exposure of metformin (a substrate of OCT1, OCT2, OCT3, MATE1, and MATE2-K) following coadministration with trilaciclib was the main interaction of note. Based on these findings, the trilaciclib US prescribing information recommends avoiding concomitant use with certain OCT2, MATE1, and MATE-2K substrates with narrow therapeutic windows [1], as an increase in exposure could potentially increase the risk of serious AEs. This is important to consider as cisplatin (but not carboplatin), which is on-label for trilaciclib and can be expected to be used for ES-SCLC treatment, is a substrate of each of these transporters [41]. As coadministration with trilaciclib may increase cisplatin exposure and alter its accumulation in the kidney, patients receiving trilaciclib concurrently with cisplatin should be monitored closely for nephrotoxicity [35]. By contrast, there were no clinically significant differences in topotecan (a MATE1 and MATE-2K substrate) clearance when used concomitantly with trilaciclib. Overall, these findings add to the evidence base indicating a favorable safety profile for trilaciclib and support the continued use of trilaciclib to decrease the incidence of chemotherapy-induced myelosuppression in adult patients with ES-SCLC.

5 Conclusions

Evaluation of the potential for DDIs between trilaciclib and midazolam (a CYP3A substrate), metformin (an OCT2, MATE1, and MATE-2K substrate), rifampin (a strong CYP3A inducer), and itraconazole (a strong CYP3A inhibitor) in healthy volunteers revealed that concomitant administration of trilaciclib had no clinically meaningful effect on midazolam pharmacokinetics but increased exposure and decreased renal clearance of metformin. No clinically meaningful differences in trilaciclib pharmacokinetics were observed when used concomitantly with itraconazole or rifampin. Coadministration of trilaciclib with midazolam, metformin, rifampin, or itraconazole was generally well tolerated. A popPK analysis identified no significant effect of trilaciclib dose or exposure on topotecan clearance in patients with ES-SCLC.

Declarations

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