Evaluation of Ipatasertib Interactions with Itraconazole and Coproporphyrin I and III in a Single Drug Interaction Study in Healthy Subjects

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**Abbreviations:** BCRP, breast cancer resistance protein; CCK-8, [3H]-Cholecystokinine-8; CP, coproporphyrin; DDI, drug-drug interaction; E$_2$17βG, [3H]-estradiol-17β-glucuronide; ITZ,
itraconazole; MDCK, madin-darby canine kidney; NMQ, N-methyl-quinidine; OATP, organic anion transporting polypeptide; P-gp, P-glycoprotein; rCYP, recombinant cytochrome P450; TEAE, treatment-emergent adverse events

**Recommended Section Assignment:**

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Abstract

Ipatasertib is a pan-AKT inhibitor in development for the treatment of cancer. Ipatasertib was metabolized by CYP3A4 to its major metabolite, M1 (G-037720), and was a P-gp substrate and OATP1B1/1B3 inhibitor in vitro. A Phase I drug-drug interaction (DDI) study (n=15) was conducted in healthy subjects to evaluate the effect of itraconazole (200 mg solution QD, 4 days), a strong CYP3A4 and P-gp inhibitor, on pharmacokinetics of ipatasertib (100 mg single dose). Itraconazole increased the C_{max} and AUC_{0-\infty} of ipatasertib by 2.3- and 5.5-fold, respectively, increased the half-life by 53% and delayed the t_{max} by 1 hour. The C_{max} and AUC_{0-72h} of M1 (G-037720) reduced by 91% and 68%, respectively. This study confirmed that CYP3A4 plays a major role in ipatasertib clearance. Furthermore, the interaction of ipatasertib with coproporphyrin (CP)I and CPIII, the two endogenous substrates of OATP1B1/1B3, was evaluated in this study. CPI and CPIII plasma levels were unchanged in the presence of ipatasertib, both at exposures of 100 mg and at higher exposures in combination with itraconazole. This indicated no in vivo inhibition of OATP1B1/1B3 by ipatasertib. Additionally, it was shown that CPI and CPIII were not P-gp substrates in vitro and itraconazole had no effect on CPI and CPIII concentrations in vivo. The latter is an important finding because it will simplify interpretation of future DDI studies using CPI/CPIII as OATP1B1/1B3 biomarkers.
Significance Statement

In this drug-drug interaction study in healthy volunteers, we demonstrated that CYP3A4 plays a major role in ipatasertib clearance, and that ipatasertib is not an OATP1B1/1B3 inhibitor. Furthermore, it was demonstrated that itraconazole, an inhibitor of CYP3A4 and several transporters did not affect CPI/CPIII levels in vivo. This increases the understanding and application of these endogenous substrates as well as itraconazole in complex drug interaction studies.
**Introduction**

Ipatasertib (GDC-0068) is a novel, potent, highly selective small-molecule inhibitor of the three isoforms of serine/threonine kinase Akt (Akt1, Akt2, and Akt3) (Blake et al., 2012; Lin et al., 2013; Yan et al., 2013) or protein kinase B. It is being developed to be used in combination with chemotherapy, hormonal agents, or targeted agents for the treatment of breast and prostate cancers (Kim et al., 2017; de Bono et al., 2019).

*In vitro* assessments of drug metabolizing enzyme- and transporter-mediated pharmacokinetic drug-drug interactions (DDI) were conducted with ipatasertib as patients with breast and prostate cancers may often require concomitant medications. Here we present both the in vitro metabolism and transport studies as well as the clinical DDI study conducted to assess the clinical impact. *In vitro*, ipatasertib is primarily metabolized by cytochrome P450 (CYP) 3A4. An N-dealkylated metabolite, M1 (G-037720), which circulates at concentrations of approximately 40% of the parent drug at steady state, is formed via CYP3A4 (Figure S1). Ipatasertib is also a substrate of the efflux transporter, P-glycoprotein (P-gp), but not a substrate of breast cancer resistance protein (BCRP) in vitro. Inducers of clearance pathways can reduce systemic exposures of the substrates of those pathways and inhibitors can increase the systemic exposures (Venkatakrishnan et al., 2000; Prueksaritanont et al, 2016). Accordingly, enzalutamide, a potent CYP3A4 inducer was co-administered with ipatasertib, it reduced exposure of ipatasertib by ~50% (Isakoff et al. 2020). Similarly, co-administering inhibitors of CYP3A4 and P-gp may increase the systemic exposure of ipatasertib.
Furthermore, an in vitro transporter inhibition assay showed that ipatasertib was a weak inhibitor of organic anion transporting polypeptide (OATP) 1B1 and OATP1B3, with ≤ 25% increase in the exposure of a substrate predicted due to inhibition of either transporters. OATP1B1 and OATP1B3 play a crucial role in the hepatic uptake of both endogenous compounds and drugs such as statins (Liu et al., 2018). Regulatory authorities have provided detailed recommendations on evaluation of clinical DDI related to OATP1B1/1B3 (FDA, 2007; EMA, 2012; PMDA, 2018) if the expected increase in exposure of substrates is >4 and 10% (AUCR cut off values of 1.04 for EMA and 1.1 for the FDA and PMDA). Recent research has identified coproporphyrin (CP) I and CPIII, the porphyrin metabolites from heme synthesis, as promising endogenous biomarkers for OATP activity (Lai et al., 2016) and can aid in assessing the effect of OATP1B1/1B3 inhibition in vivo. Evaluation of CPI and CPIII as endogenous biomarkers can assist in further understanding the need for a clinical DDI study.

To investigate the in vivo effect of CYP3A and P-gp inhibition on ipatasertib, a dedicated DDI study with itraconazole (ITZ), a strong dual CYP3A4 and P-gp inhibitor, was conducted. Within this same study, the effect of ipatasertib on the plasma levels of CPI and CPIII were assessed to evaluate the in vivo significance of in vitro OATP1B1/OATP1B3 inhibition observed with ipatasertib. A DDI between ITZ and ipatasertib was expected to increase ipatasertib exposure. Therefore, to evaluate the effect of increased ipatasertib exposure on OATP activity, CPI and CPIII exposures were measured when ipatasertib was coadministered with ITZ. Given that ITZ is a P-gp inhibitor, an in vitro P-gp vesicular transport experiment was performed with CPI and CPIII in order to rule out any role of P-gp in CPI and CPIII disposition. Additionally, the in vivo effect of ITZ on CPI and CPIII exposure was investigated in vivo.
Materials and Methods

In vitro CYP3A4 and P-gp substrate assay for ipatasertib

CYP3A4 substrate assay

To identify the CYP isoforms responsible for the metabolism of ipatasertib, pooled human liver microsomes (Corning, Tewksbury, MA) were incubated with ipatasertib in the presence or absence of chemical inhibitors of specific CYP isoforms. Selective CYP inhibitors (furafylline for CYP1A2, trancylcypromine for CYP2A6, ticlopidine for CYP2B6, quercetin for CYP2C8, sulfaphnazole for CYP2C9, ticlopidine for CYP2C19, quinidine for CYP2D6, ketoconazole for CYP3A4/5) or CYP inactivators (troleandomycin and 1-aminobenzotriazole) were pre-incubated with human liver microsomes and NADPH for 5 or 15 minutes at 37°C with NADPH (1 mM). Reactions were initiated with the addition of ipatasertib. Samples were collected from each HLM reaction at the 0- and 60-minute timepoints, centrifuged and the supernatant was analyzed for ipatasertib and M1 (G-037720) by liquid chromatography−mass spectrometry (LC/MS/MS).

Recombinant cytochrome P450 (rCYP) assay

Various rCYP isoforms (rCYP1A2, rCYP2A6, rCYP2B6, rCYP2C8, rCYP2C9, rCYP2C18, rCYP2C19, rCYP2D6, 4CYP2E1, rCYP3A4 and rCYP3A5) were used as a qualitative assessment for the formation of the metabolites. rCYP (40 pmol/mL) and NADPH were pre-incubated for 5 minutes at 37°C. The reaction was initiated with the addition of ipatasertib (1 µM) and quenched after 60 minutes. Samples were centrifuged, and the supernatant was analyzed by LC/MS/MS. Formation of M1 (G-037720) was monitored after incubations of ipatasertib with various rCYP isoforms.

P-gp and BCRP substrate assay
To assess if ipatasertib was a substrate of P-gp and BCRP, Madin-Darby canine kidney (MDCK) II transfected with human MDR1 gene (MDCKII-MDR1) or human BCRP gene (MDCKII-BCRP) were used. Monolayer assay was performed at three concentrations of ipatasertib (0.2, 2 and 60 µM, representing a range bracketing expected maximal plasma concentration of ~1.56 µM). The highest concentration represented the maximum tolerated concentration in the assay. Briefly, assay buffer containing ipatasertib in the presence and absence of PSC833 (P-gp inhibitor) (Solvo Biotechnology, Szeged, Hungary) or Ko134 (BCRP inhibitor) was added to the appropriate apical or basolateral chamber and incubated at 37°C. Digoxin or prazosin (Sigma-Aldrich, St Louis, MO) efflux ratio was determined as a positive control for MDR1 or BCRP function, with and without PSC833. Ipatasertib or control samples were taken from the receiver chambers at 0 and 120 minutes to determine the amount that permeated through the monolayer. Ipatasertib samples were analyzed by LC-MS/MS, while [3H]-digoxin and [3H]-prazosin (Perkin Elmer, Waltham, MA) were analyzed by liquid scintillation counting.

**In vitro inhibitory assay of ipatasertib on Uptake activity of OATP1B1/3**

The effect of ipatasertib on OATP1B1 and OATP1B3-mediated transport was determined using intracellular accumulation of the probe substrates, [3H]-estradiol-17β-glucuronide (E217βG) and [3H]-Cholecystokinin-8 (CCK-8), respectively, in HEK293K cells overexpressing either OATP1B1 or OATP1B3 in the presence of ipatasertib as previously described (Sane et al., 2020).

**Cell culture**
HEK293 cells were transfected with vectors containing cDNA for OATP1B1, OATP1B3 or vectors only by Solvo Biotechnology, Inc (Szeged, Hungary). HEK293 cells overexpressing OATP1B1, OATP1B3 and empty vector were cultured in Dulbecco’s Modified Eagle Medium supplemented with fetal bovine serum (8.9%), antibiotic/antimycotic (0.89%), and L-glutamate (1.79 mM) in a humidified culture chamber (37 ± 1°C, 95±5% relative humidity, and 5±1% CO₂). The medium was replaced every 2 to 3 days and the cells were passaged when they became confluent.

**OATP Inhibition Assay**

Ipatasertib, E₂17βG (Sigma-Aldrich, St Louis, MO) and CCK-8 (Sigma-Aldrich, St Louis, MO) were prepared in dimethyl sulfoxide (DMSO) spiked into incubation medium at 0.1% DMSO. The cells were plated onto standard 96-well tissue culture plates in cell culture medium 1 to 3 days prior to the experiment. OATP1B- and OATP1B3-expressing and control cells were incubated with butyric acid for 24 hours prior to the experiment to inhibit suppression of the transporter. Incubations of HEK293 cells were carried out in incubation medium (HK buffer).

Prior to the experiment, the cells were rinsed once with 1 mL of incubation medium. Cells were then pre-incubated with 0.3 mL of incubation medium containing ipatasertib or solvent control. After 15 minutes, the medium was replaced with incubation medium containing 50 nM of E₂17βG (OATP1B1) or CCK-8 (OATP1B3) and ipatasertib or solvent control. After 3 (OATP1B1) or 10 minutes (OATP1B3), incubation medium was removed and the cells were rinsed once with 1 mL of ice-cold phosphate-buffered saline containing 0.2% bovine serum albumin and twice with ice-cold phosphate buffered saline. The cells were then lysed with 0.5 mL of 0.1 M sodium hydroxide. Aliquots of the cell lysate were transferred to a 96-well plate,
diluted with scintillation fluid and analyzed on a MicroBeta2 liquid scintillation counter (Perkin Elmer, Waltham, MA). The amount of protein in each incubation was determined by bicinchoninic acid analysis.

**CPI and CPIII P-gp vesicular transport experiment**

CPI and CPIII were tested at 2.5 and 10 nM using the Solvo PREDIZEV™ MDR1 Vesicular Kit in accordance with the protocol with minor modifications (Solvo Biotechnology, Szeged, Hungary). Briefly, CPI, CPIII, and N-methyl-quinidine (NMQ) (positive control, Heredi-Szabo et al. 2013) were added to the plate containing vesicles and allowed to equilibrate for 15 minutes at 37°C. The reaction was initiated by adding the ATP and AMP solutions. The plate was gently mixed on a plate shaker and placed in a 37°C incubator. At 5, 10, and 20 minutes, 200 uL of ice-cold wash buffer was added to vesicle samples to quench the reaction. All solution was transferred to a pre-wetted filter plate and vacuum (~6 psi) was applied until all liquid was removed. Wells were washed 5 times with 200 uL of wash buffer. Methanol/water (70:30, V/V) containing 100 nM propranolol as internal standard was added to lyse the vesicles. CPI and CPIII samples were transferred to a clear bottom plate and were read on a SpectaMax i3 plate reader using an excitation wavelength of 390 nm and an emission wavelength of 621. NMQ samples were analyzed based on Solvo’s protocol. Samples were injected onto a Phenomenex XB C18 column (50 x 2 mm) using water with 0.1% formic acid (mobile phase A) acetonitrile with 0.1% formic acid (mobile phase B). Elution was carried out under gradient conditions (acetonitrile with 0.1% formic acid). Samples were quantified using ESI+ and MRM mode on a Sciex 5500 Qtrap using the MRM mode with the transition 339 -> 160.
Clinical DDI study

A Phase 1, single-center, open-label, two-period, fixed-sequence, DDI study in healthy subjects was conducted to evaluate the effect of ITZ on the pharmacokinetics (PK) of ipatasertib and its primary metabolite M1 (G-037720). The protocol, informed consent forms, and any other information given to the subjects were submitted to the Institutional Review Board for review and approved before the study was initiated. Written informed consent for the study was obtained from all subjects before protocol-specific procedures were carried out.

Study Population and Design

Healthy males and females (non-pregnant or non-lactating, and must be postmenopausal or surgically sterile or agree to use contraception from 10 days prior to study conduct until 30 days following the last dose of the study drug) who aged 18-55 years were screened to assess their eligibility to participate in the study within 26 days prior to study entry. Subjects were not allowed any concomitant medications from 14 days prior to the study. Foods known to affect CYP3A4, such as grapefruit juice, were also prohibited. Eligible subjects were admitted to the study site on the day prior to the first ipatasertib dosing (Day -1) to collect baseline data for CPI and CPIII. All enrolled subjects were administered single oral doses of ipatasertib (100 mg) on two study days (with or without coadministration of ITZ). Dosing details were as follows (Figure 1):

On Day 1 of Period 1, subjects received a single oral 100-mg tablet of ipatasertib after at least an 8-hour fast, followed by a washout period of approximately 14 days between dosing on Day 1 (Period 1) and Day 15 (Period 2). On Day 15 through Day 23 (Period 2), subjects received oral 200-mg ITZ dose QD (20 mL x 10 mg/mL solution; QD) and on Day 19 (Period 2) ITZ was
coadministered with a single oral 100-mg ipatasertib dose after at least an 8-hour fast. Doses (ipatasertib and ITZ) were followed by at least a 4 hours postdose fast. For each dose, except as part of dose administration, subjects were restricted from consumption of water for 1 hour prior to dose and for 2 hours postdose; at other times during the study, subjects consumed water ad libitum.

To assess the safety and tolerability of ipatasertib and ITZ, physical examinations, 12-lead electrocardiograms, vital signs, clinical laboratory evaluations, and recording of adverse events were performed at screening, at specified times during the study and at follow-up or study completion and/or at early termination.

**Plasma Samples Collection**

Serial blood samples were collected for the determination of ipatasertib and M1 (G-037720) concentrations on Days 1 to 7 (Period 1; 0, 0.167, 0.5, 1, 2, 3, 4, 6, 8, 12, 24, 36, 48, 72, 96, 120 and 144 hours) and on Days 19 through 27 (Period 2; 0, 0.167, 0.5, 1, 2, 3, 4, 6, 8, 12, 24, 36, 48, 72, 96, 120, 144, 168 and 192 hours). Blood samples were collected for the determination of ITZ and its metabolite 1-hydroxyitraconazole concentrations on Day -1 (Period 1; baseline) and on Days 18 and 19 (Period 2; postdose). Serial blood samples were also collected for the determination of OATP biomarker CPI and CPIII concentrations over 24 hours prior to first ipatasertib dosing starting on Day -1 through 24 hours postdose on Day 2 (Period 1) and on Days 18 and 19 (Period 2) prior to the second ipatasertib dose coadministered with ITZ.

**Bioanalysis of Plasma samples, PK and Statistical Analyses**
Plasma concentrations of ipatasertib, M1 (G-037720), ITZ, and 1-hydroxyitraconazole were determined using a validated assay using supported-liquid extraction and high-performance liquid chromatography coupled with tandem mass spectrometric detection. CPI and CPIII plasma concentrations were determined by a qualified bioanalysis assay using liquid-liquid extraction and high-performance liquid chromatography-tandem mass spectrometry with multiple reaction monitoring and electrospray ionization in the positive mode by Covance Laboratories, Inc (Madison WI), (Liu et al., 2018). The LC–MS/MS analysis was carried out with an ACE C18 Column (3 µm, 50 × 3 mm) on a Shimadzu HPLC system coupled with a Sciex API 5000 mass spectrometer. Chromatographic separation was performed under gradient conditions with a mobile phase composed of 10 mM ammonium formate (Mobile Phase A) and methanol (Mobile Phase B). Ipatasertib, M1 (G-037720), ITZ, 1-hydroxyitraconazole and CPI/CPIII were monitored by m/z 460.2 → 389.2; 416.2 → 217.2; 707.4 → 392.3; 721.4 → 408.3; and 655.3 → 596.3, respectively. Assay employed deuterated internal standards for ipatasertib, M1, ITZ and 1-hydroxy itraconazole or stable labeled internal standards for coproporphyrin. The LLOQ for ipatasertib and M1 was 0.463 ng/mL, LLOQ for ITZ and 1-hydroxy itraconazole was 5 ng/mL, LLOQ for CPI was 50 ng/mL and LLOQ for CPIII was 20 ng/mL.

The following PK parameters were derived from plasma concentrations of ipatasertib and M1 (G-037720) using the noncompartmental methods: C\text{max}, t\text{max}, AUC\text{0-tz}, AUC\text{0-}\infty, t\text{1/2}, CL/F (ipatasertib only), V_{z}/F (ipatasertib only), metabolite ratio based on metabolite and parent C\text{max} and AUC. For CPI and CPIII analysis, C\text{max}, t\text{max} and AUC\text{0-tz} were determined. PK calculations were performed using commercial software Phoenix WinNonlin (Certara Inc., version 6.4 or higher). For the primary analysis of DDI with ITZ, the effect of ITZ on ipatasertib and M1 (G-037720) PK was assessed. Natural log-transformed C\text{max}, AUC\text{0-t}, and AUC\text{0-}\infty values for ipatasertib were compared between Period 1 (reference; ipatasertib alone) and Period 2 (test; ipatasertib plus ITZ).
using a mixed effects model with treatment as a fixed effect and subject as a random effect. A point estimate and the corresponding 90% confidence intervals (CI) for the difference between least squares mean of the log-transformed $C_{\text{max}}$, $\text{AUC}_{0-t}$, and $\text{AUC}_{0-\infty}$ with and without coadministration of ITZ were calculated and used to determine the presence of a DDI. For the analysis related to OATP1B1/1B3 inhibition, $\text{AUC}_{0-24}$ and $C_{\text{max}}$ for CPI and CPIII were also compared in a similar way. All calculations were performed using SAS® version 9.3 or greater.
Results

In vitro metabolism of ipatasertib to M1 (G-037720)

HLM in the presence of selective chemical inhibitors and human rCYP isoforms were used to identify the major human CYP isoforms responsible for the metabolism of ipatasertib and formation of M1 (G-037720). Metabolism of ipatasertib in HLM was inhibited by CYP3A selective inhibitor, ketoconazole, as well as troleandomycin by >94% but not other CYP450 inhibitors. These selective CYP3A inhibitors inhibited the formation of M1 (G-037720), suggesting CYP3A was the major contributor to the metabolism of ipatasertib. Incubation of ipatasertib with several recombinant CYP isoforms (rCYP1A2, rCYP2B6, rCYP2C9, rCYP2C19, rCYP2D6, rCYP3A4, rCYP3A5) confirmed that CYP3A4 was the primary CYP responsible for the formation of M1 (G-037720). M1 itself had very low turnover in vitro. Reaction phenotyping results are reported in Table S1 in the supplemental file.

In vitro P-gp substrate assay

Ipatasertib incubated at 0.2, 2 and 60 µM in MDCKII-MDR1 monolayers resulted in efflux ratios of 1.41, 6.14 and 12.64, respectively, which reduced to 1.20, 1.78 and 1.73 in the presence of the P-gp inhibitor, PSC833. These results suggested that ipatasertib was a substrate of P-gp. Results are shown in Figure S2 in the supplemental file.

In vitro BCRP substrate assay

Ipatasertib incubated at 0.2, 2 and 60 µM in MDCKII-BCRP monolayers resulted in efflux ratios of > 6. The presence of BCRP inhibitor Ko134 did not significantly reduce the efflux, however the P-gp inhibitor, PSC833 reduced the efflux ratio to 1. This suggests the efflux observed was due to endogenous canine Mdr1 present in the cell line and not due to BCRP. Results are shown in Figure S3 in the supplemental file.
In vitro inhibitory assay of ipatasertib on uptake activity of OATP1B1/3

Ipatasertib inhibited the OATP1B1- and OATP1B3-mediated transport of E217G and CCL-8, respectively, in a dose-dependent manner (Figure 2). The calculated IC$_{50}$ values were 141.5 µM and 191.1 µM for OATP1B1 and OATP1B3, respectively. Rifampicin (50 µM) was used as a positive control and at this concentration it completely inhibited OATP1B1 and 1B3 mediated uptake.

CPI and CPIII P-gp vesicular transport experiment

The mean uptake of CPI and CPIII in MDR1 membrane vesicles in the presence of AMP and ATP were determined and demonstrated no active uptake (Figure 3). Two concentrations of CPI and CPIII were tested (2.5 nM and 10 nM), and no significant differences in the transport of CPI and CPIII at both tested concentrations were observed in the presence and absence of ATP. The positive control, NMQ, demonstrated marked uptake.

Clinical DDI study

Demographics and Other Baseline Characteristics of Subjects

Fifteen subjects were enrolled in and completed the study. The median (range) age of all enrolled subjects was 36 years (22 to 52 years). Majority of the subjects were female (66.7%), white (53.3%), and Hispanic or Latino (60.0%). The median (range) BMI for enrolled subjects was 24.88 kg/m$^2$ (20.69 to 30.24 kg/m$^2$).

Ipatasertib Pharmacokinetics in the absence and presence of itraconazole
Ipatasertib $C_{\text{max}}$ and AUC both showed a marked increase in presence of ITZ (Figure 4, Table 1). The $t_{\text{max}}$ appeared slightly delayed and the arithmetic mean $t_{1/2}$ was 23 hours longer (approximately 53% increase) when ipatasertib was coadministered with ITZ versus alone. Statistical analysis to evaluate the effect of ITZ on the PK of ipatasertib yielded geometric LS means ratios (90% CIs) of approximately 545% (496% to 598%) and 226% (183% to 280%) for AUC$_{0-\infty}$ and $C_{\text{max}}$, respectively (Table 2). That is, AUC$_{0-\infty}$ and $C_{\text{max}}$ of ipatasertib increased by 5.45 fold and 2.26 fold, respectively.

Following single-dose oral administration of ipatasertib 100 mg alone, absorption of ipatasertib was rapid with detectable plasma concentrations for most subjects observed at the first sampling timepoint (Figure 4 and Table 1). Following oral dosing of ipatasertib 100 mg coadministered with ITZ 200 mg, first detectable concentrations of ipatasertib were not observed until approximately 30 minutes postdose. Geometric mean CL/F and $V_z/F$ values decreased by approximately 82% and 72%, respectively, following ipatasertib coadministered with ITZ versus ipatasertib alone.

**Metabolite M1 (G-037720) Pharmacokinetics**

Similar to the parent, M1 (G-037720) PK altered when ipatasertib was administered with ITZ, with $C_{\text{max}}$ and AUC both showing marked decrease in presence of ITZ (Figure 4 and Table 3). Arithmetic mean $t_{1/2}$ of M1 (G-037720) were 36.0 hours and 47.6 hours when ipatasertib was coadministered with ITZ versus ipatasertib alone, respectively. Statistical analysis to evaluate the effect of ITZ on the PK of M1 (G-037720) yielded geometric LS means for AUC$_{0-72}$ and $C_{\text{max}}$ of approximately 68% and 91%, respectively (Table 2). Coadministration of ipatasertib with ITZ...
decreased the geometric mean metabolic ratios (MR$_{\text{Cmax}}$, MR$_{\text{AUC0-∞}}$, and MR$_{\text{AUC0-72}}$) by approximately 25-, 12-, and 15-fold, respectively (Table 3).

Following single-dose oral administration of ipatasertib 100 mg alone, M1 (G-037720) detectable plasma concentrations appeared within 30 minutes for most subjects (Figure 4 and Table 3). Whereas following oral dosing of ipatasertib 100 mg coadministered with ITZ 200 mg, first detectable concentrations of M1 (G-037720) were not observed for most subjects until approximately 2 hours postdose. Median t$_{\text{max}}$ appeared delayed by about 6 hours when ipatasertib was coadministered with ITZ compared to ipatasertib alone (Table 3).

**Pharmacokinetic Results for Itraconazole and Metabolite 1-Hydroxyitraconazole**

Plasma concentrations of ITZ and its primary metabolite (1-hydroxyitraconazole) were measured predose and postdose on day 18 (4th consecutive day of ITZ dosing) over a 24-hour period. Following administration of ITZ, geometric mean (geometric CV%) C$_{\text{max}}$ and median (min, max) t$_{\text{max}}$ for ITZ were 1640 ng/mL (17.5%) and 3.00 (2.00, 4.03) hours, respectively. In general, geometric mean ITZ trough (predose) concentrations on days 18 and 19 were similar (313 and 383 ng/mL, respectively). For 1-hydroxyitraconazole, geometric mean (geometric CV%) C$_{\text{max}}$ and median (min, max) t$_{\text{max}}$ were 1280 ng/mL (15.6%) and 4.00 (3.00, 5.00) hours, respectively.

**CPI and CPIII plasma levels**

Ipatasertib, at the exposures achieved in this study with or without ITZ, did not cause any changes in CPI and CPIII plasma levels (Figure 5, Table 4, Table 5). ITZ administration also did not alter the CPI and CPIII plasma levels (Figure 5, Table 4).
Summary of Adverse Events

Overall, both ipatasertib and ITZ were well tolerated when given alone or in combination to the healthy male and female subjects in this study. All treatment-emergent AEs (TEAEs) were assessed by the Investigator as mild (Grade 1) in intensity and resolved by the end of the study. Three subjects had TEAEs that were assessed by the investigator as related to ipatasertib; these TEAEs considered related to ipatasertib were nausea. Four subjects had TEAEs that were assessed by the investigator as related to ITZ; these TEAEs considered related to ITZ included nausea (3 subjects) and diarrhea, dysgeusia, headache, and disorientation (1 subject each). No clinically significant changes from baseline or findings were noted from clinical laboratory evaluations, vital signs measurements, or 12-lead ECGs for this study.

Discussion

Itraconazole had a marked impact on PK of ipatasertib: ipatasertib exposure (AUC\(_{0-\infty}\)) increased by 5.45-fold, the mean t\(_{1/2}\) increased by 53% and the CL/F decreased by 82% in the presence of itraconazole. Ipatasertib is a substrate of both CYP3A4 and P-gp in vitro and the results are consistent with the inhibition of CYP3A4 and P-gp mediated clearance by itraconazole. The inhibitory effect of itraconazole on CYP3A4 versus P-gp cannot be differentiated easily; however, the impact of itraconazole on M1 (G-037720), the major metabolite of ipatasertib, can provide additional insights. The C\(_{\text{max}}\) and the AUC\(_{0-72}\) of M1 (G-037720), a metabolite formed primarily via CYP3A4, decreased by 91% and 68%, respectively, suggesting CYP3A4 has a major role in the elimination of ipatasertib and may be the main mechanism underlying the DDI. This also lends additional support to the observation that M1 follows formation rate limited
kinetics apparent from the similar half-lives of ipataserib and M1 when ipatasertib is administered alone.

Itraconazole also appeared to impact the $t_{\text{max}}$ of ipatasertib. The first detectable concentration and median $t_{\text{max}}$ of ipatasertib was slightly delayed in the presence of itraconazole. This observation did not appear to be an artifact of sampling times or an anticipated effect of itraconazole-mediated CYP3A and P-gp inhibition. Given that the range of $t_{\text{max}}$ overlapped between the two treatment groups, it is likely that this observation was attributed to the high variability of ipatasertib PK. Also, for M1 (G-037720), the $t_{1/2}$ values should be interpreted with caution as there were a limited number of quantifiable concentrations available to include in the estimation of the terminal rate constant. The apparent change in $Vz/F$ in presence of itraconazole is likely due to reduced first pass effect and therefore, a change in oral bioavailability (F).

Given the magnitude of the observed DDI, the coadministration of other strong CYP3A4 inhibitors such as posaconazole, clarithromycin, and grapefruit juice are being avoided in clinical studies with ipatasertib or used with a reduced dose of ipatasertib (https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers). In this study a 100 mg single dose of ipatasertib was administered, which is lower than the intended therapeutic dose of 400 mg. At 400 mg, the magnitude of DDI is expected to be somewhat lower than that observed at 100 mg as the competition for CYP3A4 is typically concentration dependent. Physiologically based PK (PBPK) modeling is ongoing to predict the DDI at 200 and 400 mg dose of ipatasertib to provide guidance for use with weak and moderate inhibitors of CYP3A4.
The PK of itraconazole and its primary metabolite, 1-hydroxyitraconazole, were also assessed in this study to ensure sufficient inhibitor concentrations were achieved. The $C_{\text{max}}$ and $t_{\text{max}}$ of itraconazole were comparable to that previously observed following administration of 200 mg itraconazole oral solution under fasted conditions for 15 days at 1963 ng/mL and 2.5 hours, respectively (Sporanox oral solution USPI). The $C_{\text{max}}$ of 1-hydroxyitraconazole observed on day 18 in this study was slightly lower than that previously reported; however, the geometric mean concentrations of itraconazole and 1-hydroxyitraconazole were well above the reported IC$_{50}$ values (approximately 29 nM [20.5 ng/mL] and 37 nM [26.7 ng/mL], respectively), indicating they provided sufficient inhibition of CYP3A4 in this study (Isoherranen et al., 2004).

Initial single or multiple ascending dose studies may often be desired to evaluate the effect of a drug on endogenous biomarkers. However, ipatasertib is in late stages of clinical development with several patient studies ongoing in combination with other agents (Kim et al., 2017; de Bono et al., 2019). This study in healthy subjects was considered suitable to evaluate the in vivo effect of ipatasertib on OATP1B1/1B3 since ipatasertib was given as a single agent. In typical oncology clinical studies, patients are taking other comediations that can confound DDI study results. Therefore, it was important to have a study population with minimal confounder effects as there was expected to be minimal or no effect of ipatasertib inhibition on OATP1B1/1B3 in vivo. Any confounding effects due to comediations could have made the results inconclusive. Based on in vitro predictions using the methods described in the FDA DDI guidance, at the clinically intended dose of 400 mg, and the observed IC$_{50}$ values, the predicted AUC ratios (AUC in presence of inhibitor/AUC in absence of inhibitor), using the estimated maximum unbound liver inlet concentration ($I_{\text{inlet,unbound}}$) of ipatasertib and default values for $Fa$, $Fg$ and $Ka$
(as worst case scenario), were calculated to be 1.25 and 1.19 for OATP1B1 and OATP1B3 inhibition, respectively. These are slightly higher than the FDA cutoff of 1.1 (FDA DDI guidance). However, when using a realistic Ka value estimated from population PK analysis of ipatasertib (data on file) to calculate the maximum unbound liver inlet concentration, these ratios were 1.08 and 1.06, respectively, for OATP1B1 and OATP1B3, less than the FDA cutoff of 1.1. Therefore, this CYP3A4 DDI study was leveraged to measure the changes in CPI and CPIII levels before and after administration of ipatasertib. As expected, after 100 mg ipatasertib administration, no change was observed in CPI and CPIII exposures, which were surrogates for OATP1B1/1B3 activity.

In this present clinical DDI study, subjects received 100 mg ipatasertib, which was lower than intended clinical dose of 400 mg (Kim et al., 2017; de Bono et al., 2019). This dose was selected for the study to minimize unnecessary drug exposure in healthy subjects, especially in anticipation of a DDI. Consequently, the exposure of ipatasertib in presence of itraconazole was comparable to the exposure observed after administration of 400 mg ipatasertib in patients. Therefore, CPI and CPIII were also evaluated in presence of both ipatasertib and itraconazole to assess the impact of ipatasertib exposures expected at intended therapeutic dose. There was no change in CPI and CPIII plasma levels even at higher ipatasertib exposures, indicating ipatasertib did not inhibit OATP1B1/1B3 in vivo at the clinically relevant exposures. Following administration of ipatasertib alone, itraconazole alone, or coadministration of ipatasertib with itraconazole, AUC$_{0-tz}$ and C$_{\text{max}}$ of CPI and III were generally similar to the respective values at baseline (maximum decreases of $\leq$11% from baseline). Given that itraconazole also did not impact CPI and CPIII exposure, the conclusion that ipatasertib did not impact CPI and CPIII
levels when coadministered with itraconazole was not confounded. Overall, OATP1B1/1B3 substrates can be coadministered with ipatasertib without a risk of DDI even at clinically relevant concentrations of ipatasertib.

To facilitate interpretation of CPI and CPIII data, an uptake experiment was prospectively conducted which demonstrated that neither CPI nor CPIII were substrates of P-gp. Itraconazole, a P-gp inhibitor, did not alter CPI and CPIII levels in our study, and this is consistent with an observed lack of P-gp involvement in CPI and CPIII transport (Figure 3). This observation was in line with previously reported *in vitro* data; CPI and CPIII have been reported as being substrates of OATP1B1/3 and the multidrug resistance-associated protein (MRP) 2 and MRP3. CPI and CPIII were not substrates of other uptake or efflux transporters including BCRP, the bile salt export pump (BSEP), P-gp, the multidrug and toxin extrusion proteins (MATE) 1/2K, MRP4, the organic anion transporter (OAT) 1/3, the organic cation transporter (OCT) 1/2 and the sodium taurocholate co-transporting polypeptide (NTCP) (Kunze et al., 2018).

The observation that CPI and CPIII levels were not altered in a clinical setting by the presence of itraconazole, which is an inhibitor of CYP3A4, P-gp and BCRP, adds to the scientific knowledge in the field of transporter-mediated DDI. Itraconazole has been shown to increase the concentration of OATP1B1/1B3 substrates such as rosuvastatin and pravastatin in previous studies (Vaidyanathan et al. 2016). However, the lack of effect on CPI and CPIII in our study suggests inhibition of other transporters such as P-gp and/or BCRP by itraconazole and/or 1-hydroxyitraconazole may be playing a role in the DDI studies with statins. If a new molecule is an inhibitor of CYP3A4 and multiple transporters such as P-gp, BCRP and OATP1B1/1B3, CPI
and CPIII offer an appropriate option to evaluate an exclusive effect on OATP1B1/1B3 as compared to probe substrates such as atorvastatin, rosuvastatin or simvastatin, which are substrates of these other enzymes or transporters. This study demonstrates, in a clinical setting, that CPI and CPIII exposures are not affected by itraconazole, a CYP3A4, P-gp and BCRP inhibitor. These results make interpretation of itraconazole DDI studies simpler, when the victim molecules are substrates of multiple transporters, such as fexofenadine (Shimizu et al., 2006). This type of study design also offers the flexibility to evaluate CPI and CPIII at a higher concentration of the inhibitor drug, which may be needed for studying complex DDI or DDI in special populations, scenarios in which higher drug exposures may occur. Itraconazole can boost perpetrator concentrations which may aid CPI and CPIII evaluation at a higher inhibitor concentration without any interference.

Overall, using this approach of evaluating two DDIs in one study, has provided evidence that ipatasertib is a substrate of CYP3A4 in vivo and therefore a victim of DDI with strong CYP3A4 inhibitors, and that ipatasertib does not inhibit OATP1B1/1B3 in vivo. As polypharmacy is not uncommon in patients with cancer, this study has provided critical information to ensure safe use of ipatasertib in patients and provides DDI risk mitigation strategies for ongoing clinical studies and future clinical use of ipatasertib. The study also offers new insights by demonstrating lack of CPI/CPIII interaction with itraconazole.
Acknowledgements

We thank the research team at Covance Inc. for conducting this study.

Authorship Contributions

Participated in research design: RS, VM, LM, BL

Conducted experiments: RS, EP, SW, EC, JH

Contributed new reagents or analytic tools: EP, RS

Performed data analysis: VM, EM, SW

Wrote or contributed to the writing of the manuscript: RS, KC, VM
References


interaction assessments for drug transporters and CYP3A. Clin Pharmacol Ther. 2017


Footnotes

All authors are employees of Genentech, Inc. All studies were sponsored by Genentech Inc.
This work was previously presented as a poster at the ACCP 2019 Annual meeting in Chicago, IL.
Figure Legends

**Figure 1:** Schematic of Study Design.

**Figure 2:** Inhibition of OATP1B1-mediated E217βG (1 µM) and OATP1B3-mediated CCK-8 (0.1 µM) transport by ipatasertib was assessed in HEK293K cells stable transfected with respective transporters. Cells were dosed with ipatasertib and vehicle (1% DMSO). The experiment was conducted for 2 minutes at 37°C for both transporters. Data are expressed as a mean (n=3) ± SD from a single experiment.

**Figure 3:** Mean uptake of CPI and III in MDR1 membrane vesicles in the presence of AMP and ATP with total vesicle protein of 50 µg/well. Ipatasertib was preinubated with vesicles for 10 minutes before the addition of ATP/AMP to start the reaction. Data are expressed as a mean (n=3) ± SD from a single experiment.

**Figure 4:** Arithmetic mean (+SD) plasma concentration-time profiles of ipatasertib (A) and the major metabolite M1 (G-037720) (B) following single-dose oral administration of ipatasertib 100 mg alone or coadministered with itraconazole 200 mg in healthy subjects (N=15).

**Figure 5:** Arithmetic mean (+SD) concentration-time profile of CPI (A) and CPIII (B) at baseline and following oral administration of ipatasertib 100 mg alone, itraconazole 200 mg alone, or co-administration of ipatasertib and itraconazole in healthy subjects (N=15).
Tables
Table 1. Summary of PK parameters of ipatasertib following single oral dose of ipatasertib 100 mg alone or co-administered with itraconazole 200 mg

<table>
<thead>
<tr>
<th>Ipatasertib PK Parameters</th>
<th>Ipatasertib (100 mg) N = 15</th>
<th>Ipatasertib (100 mg) + Itraconazole (200 mg) N = 15</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC&lt;sub&gt;0-∞&lt;/sub&gt; (ng*h/mL)</td>
<td>327 (26.4)</td>
<td>1780 (22.6)</td>
</tr>
<tr>
<td>AUC0-72 (ng*h/mL)</td>
<td>271 (25.5)</td>
<td>1300 (22.9)</td>
</tr>
<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt; (ng/mL)</td>
<td>44.9 (35.9)</td>
<td>102 (34.1)</td>
</tr>
<tr>
<td>t&lt;sub&gt;max&lt;/sub&gt; (h)</td>
<td>1.07 (0.50, 3.03)</td>
<td>2.05 (1.00, 6.00)</td>
</tr>
<tr>
<td>t&lt;sub&gt;1/2&lt;/sub&gt; (h)</td>
<td>44.0 (8.52)</td>
<td>67.2 (9.20)</td>
</tr>
<tr>
<td>CL/F (L/h)</td>
<td>306 (26.4)</td>
<td>56.2 (22.6)</td>
</tr>
<tr>
<td>Vz/F (L)</td>
<td>19100 (20.0)</td>
<td>5400 (33.9)</td>
</tr>
</tbody>
</table>

All values are reported as geometric mean (geo% CV); t<sub>max</sub> is reported as median (range); t<sub>1/2</sub> is reported as mean (SD).
Table 2. Statistical analysis of ipatasertib and M1 (G-037720) PK parameters following single oral dose of ipatasertib 100 mg alone or when co-administered with itraconazole 200 mg.

<table>
<thead>
<tr>
<th>Analyte</th>
<th>Parameter</th>
<th>GMR (90% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ipatasertib</td>
<td>AUC&lt;sub&gt;0-∞&lt;/sub&gt; (ng*h/mL)</td>
<td>545 (496, 598)</td>
</tr>
<tr>
<td></td>
<td>C&lt;sub&gt;max&lt;/sub&gt; (ng/mL)</td>
<td>226 (183, 280)</td>
</tr>
<tr>
<td>M1 (G-037720)</td>
<td>AUC&lt;sub&gt;0-72&lt;/sub&gt; (ng*h/mL)</td>
<td>31.6 (26.7, 37.6)</td>
</tr>
<tr>
<td></td>
<td>C&lt;sub&gt;max&lt;/sub&gt; (ng/mL)</td>
<td>8.9 (7.6, 10.5)</td>
</tr>
</tbody>
</table>

GMR is ratio of the least squares means from ANOVA for natural log transformed AUCs or C<sub>max</sub> (expressed as a percent), natural log was transformed back to the linear scale; Test/Reference where test = ipatasertib + itraconazole and reference = ipatasertib alone. CI (Confidence interval)
Table 3. Summary of PK parameters of M1 (G-037720) following single oral dose of ipatasertib 100 mg alone or co-administered with itraconazole 200 mg

<table>
<thead>
<tr>
<th>M1 (G-037720) PK Parameters</th>
<th>Ipatasertib (100 mg)</th>
<th>Ipatasertib (100 mg) + Itraconazole (200 mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N =15</td>
<td>N=15</td>
</tr>
<tr>
<td>AUC&lt;sub&gt;0-∞&lt;/sub&gt; (ng*h/mL)</td>
<td>233 (35.7)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>110 (57.7)&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>AUC&lt;sub&gt;0-72&lt;/sub&gt; (ng*h/mL)</td>
<td>179 (34.7)</td>
<td>58.0 (38.5)&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt; (ng/mL)</td>
<td>18.4 (42.3)</td>
<td>1.64 (29.5)</td>
</tr>
<tr>
<td>t&lt;sub&gt;max&lt;/sub&gt; (h)</td>
<td>2.03 (1.02, 3.15)</td>
<td>8.00 (2.00, 12.00)</td>
</tr>
<tr>
<td>t&lt;sub&gt;1/2&lt;/sub&gt; (h)</td>
<td>47.6 (14.0)</td>
<td>36.1 (12.7)&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>MR&lt;sub&gt;Cmax&lt;/sub&gt;</td>
<td>0.452 (50.2)</td>
<td>0.0178 (41.0)</td>
</tr>
<tr>
<td>MR&lt;sub&gt;AUC&lt;/sub&gt;</td>
<td>0.787 (19.8)</td>
<td>0.0646 (33.9)&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>MR&lt;sub&gt;AUC0-72&lt;/sub&gt;</td>
<td>0.728 (20.1)</td>
<td>0.0484 (23.7)&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
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</table>

<sup>a</sup>N=14; <sup>b</sup>N=4; All values are reported as geometric mean (geo%CV); t<sub>max</sub> is reported as median (range); t<sub>1/2</sub> is reported as mean (SD).
Table 4. Summary of parameters for CPI and CPIII at baseline and following administration of Ipatasertib 100 mg alone, Itraconazole 200 mg alone, or co-administration of Ipatasertib with Itraconazole

<table>
<thead>
<tr>
<th>Analyte</th>
<th>Parameter</th>
<th>Baseline (N=15)</th>
<th>Ipatasertib (100 mg) (N=15)</th>
<th>Itraconazole (200 mg) (N=15)</th>
<th>Ipatasertib (100 mg) + Itraconazole (200 mg) (N=15)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CPI</td>
<td>AUC&lt;sub&gt;0-24&lt;/sub&gt; (pg*h/mL)</td>
<td>13300 (3340)</td>
<td>13000 (3670)</td>
<td>11900 (3710)</td>
<td>12500 (2990)</td>
</tr>
<tr>
<td></td>
<td>C&lt;sub&gt;max&lt;/sub&gt; (pg/mL)</td>
<td>673 (146)</td>
<td>663 (200)</td>
<td>621 (192)</td>
<td>610 (141)</td>
</tr>
<tr>
<td>CPIII</td>
<td>AUC&lt;sub&gt;0-24&lt;/sub&gt; (pg*h/mL)</td>
<td>1670 (443)</td>
<td>1600 (446)</td>
<td>1580 (492)</td>
<td>1530 (499)</td>
</tr>
<tr>
<td></td>
<td>C&lt;sub&gt;max&lt;/sub&gt; (pg/mL)</td>
<td>89.8 (28.9)</td>
<td>85.7 (26.3)</td>
<td>82.4 (23.7)</td>
<td>82.0 (28.3)</td>
</tr>
</tbody>
</table>

Data are expressed as Mean (SD)
Table 5. Statistical analysis of the effect of ipatasertib on PK parameters of Coproporphyrins I and III

<table>
<thead>
<tr>
<th>Analyte</th>
<th>Parameter</th>
<th>GMR (90% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>AUC&lt;sub&gt;0-24&lt;/sub&gt; (pg* h/mL)</td>
<td>97.4 (94.0, 100.8)</td>
</tr>
<tr>
<td>Coproporphyrin I</td>
<td>C&lt;sub&gt;max&lt;/sub&gt; (pg /mL)</td>
<td>96.7 (88.4, 105.9)</td>
</tr>
<tr>
<td></td>
<td>AUC&lt;sub&gt;0-24&lt;/sub&gt; (pg* h/mL)</td>
<td>95.9 (89.6, 102.8)</td>
</tr>
<tr>
<td>Coproporphyrin III</td>
<td>C&lt;sub&gt;max&lt;/sub&gt; (pg /mL)</td>
<td>95.8 (86.4, 106.2)</td>
</tr>
</tbody>
</table>

GMR is the ratio of the least squares means from ANOVA for natural log transformed AUC<sub>0-24</sub> or C<sub>max</sub> (expressed as a percent), natural log transformed back to the linear scale; Test/Reference where test = ipatasertib 100 mg alone and reference = Baseline. CI (Confidence interval)
**Figure 1**

<table>
<thead>
<tr>
<th></th>
<th>PERIOD 1</th>
<th>WASHOUT</th>
<th>PERIOD 2</th>
</tr>
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<tr>
<td>Study Day</td>
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<td>1</td>
</tr>
<tr>
<td></td>
<td>5</td>
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<td>15</td>
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<tr>
<td></td>
<td>20</td>
<td>25</td>
<td>27</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Event</th>
<th>Study Day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ipatasertib 100 mg QD dose</td>
<td></td>
</tr>
<tr>
<td>Itraconazole 200 mg QD dose</td>
<td></td>
</tr>
<tr>
<td>Ipatasertib + metabolite PK collection</td>
<td></td>
</tr>
<tr>
<td>Itraconazole + metabolite PK collection</td>
<td></td>
</tr>
<tr>
<td>Coproporphyrins sample collection</td>
<td></td>
</tr>
</tbody>
</table>

Arrows indicate timing of events.
Figure 2.

A. Relative transport of E217/G (% of control) vs. Ipatasertib concentration (μM)

IC₅₀ = 141.5 μM

B. Relative transport of CCK-8 (% of control) vs. Ipatasertib concentration (μM)

IC₅₀ = 191.1 μM
Figure 3.

![Bar chart showing fold accumulation ATP/AMP ratio at different concentrations (2.5 nM, 10 nM, 1 μM) for different conditions (CPI, CPIII, NMQ).]
Figure 4.

A. 

Ipatasertib plasma concentration (ng/mL) over time postdose (hr).

- Lower limit of quantification
- 100 mg ipatasertib alone
- 100 mg ipatasertib + 200 mg itraconazole

B. 

M1 (G-037720) plasma concentration (ng/mL) over time postdose (hr).

- Lower limit of quantification
- 100 mg ipatasertib alone
- 100 mg ipatasertib + 200 mg itraconazole