Mitigating ipatasertib-induced glucose increase through dose and meal timing modifications

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Abstract

Ipatasertib, an AKT inhibitor, in combination with prednisone and abiraterone, is under evaluation for the treatment of metastatic castration-resistant prostate cancer (mCRPC). Hyperglycemia is an on-target effect of ipatasertib. An open-label, single-arm, single-sequence, signal-seeking study ($n = 25$ mCRPC patients) was conducted to evaluate the glucose changes across four different treatment periods: ipatasertib alone, ipatasertib-prednisone combination, ipatasertib-prednisone-abiraterone combination (morning dose), and ipatasertib-prednisone-abiraterone combination (evening dose). Continuous glucose monitoring (CGM) was used in this study to compare the dynamic glucose changes across the different treatment periods. Four key parameters: average glucose, peak glucose and % time in range (70–180 and >180 mg/dl) were evaluated for this comparison. Ipatasertib-prednisone-abiraterone combination when administered in the morning after an overnight fast significantly increased average glucose, peak glucose and % time in range >180 mg/dl compared to ipatasertib monotherapy. Ipatasertib, when co-administered with abiraterone, increased ipatasertib and M1 (G-037720) metabolite exposures by approximately 1.5- and 2.2-fold, respectively. Exposure–response analysis results show that increased exposures of ipatasertib in combination with abiraterone are associated with increased glucose levels. When ipatasertib-prednisone-abiraterone combination was administered as an evening dose compared to a morning dose, lowered peak glucose and improved % time in range was observed. The results from this study suggest that dosing ipatasertib after an evening meal followed by overnight fasting can be an effective strategy for managing increased glucose levels.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?
Clinical development of PI3K/AKT inhibitors has been particularly challenging given their toxicity profiles, hyperglycemia being one of the on-target effects.

WHAT QUESTION DID THIS STUDY ADDRESS?

This study evaluated the real-time changes in glucose levels post-ipatasertib administration using a continuous glucose-monitoring wearable device. This study further evaluated morning versus evening dosing of ipatasertib in combination with prednisone and abiraterone.

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

The results from this study suggest that offering ipatasertib, an AKT inhibitor, as an evening dose after evening meal may offer a better option at de-risking hyperglycemia incidences. The study also provides preliminary information that a low dose of steroids does not lead to a marked increase in glucose levels when administered in combination with ipatasertib.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?

This is a novel clinical pharmacology study, wherein a safety finding was investigated using an innovative continuous glucose-monitoring device and results were discussed in the context of pharmacokinetic results and drug–drug interactions. The conclusions and the methodology are supportive of further investigations to mitigate hyperglycemia risk for oncology drugs that inhibit the AKT/PI3K pathway, as this class of drugs are known to cause an increase in blood glucose.

INTRODUCTION

The phosphoinositide 3-kinase (PI3K)-AKT pathway is one of the most frequently activated pathways in prostate cancer, with genomic alterations occurring in approximately 50% of cases with genetic loss of PTEN as the most common cause.[1] Ipatasertib is a potent, highly selective, small molecule that inhibits all the three isoforms of the serine/threonine kinase AKT and has proven to be potent in nonclinical models, including PTEN-null and PI3K-mutated tumors in vitro and in vivo.[2] Literature suggests a crosstalk exists between the androgen receptor (AR) and PI3K/AKT pathways where activation of the PI3K/AKT pathway is associated with repressed androgen signaling and inhibition of the PI3K/AKT pathway restores AR signaling in PTEN-deficient prostate cells.[3,4] This reciprocal cooperativity between PI3K/AKT and AR pathways suggests inhibition of only one pathway may lead to suboptimal clinical efficacy, and therefore combined inhibition of the AR and PI3K/AKT pathways may be beneficial in achieving clinical benefit.

Ipatasertib is being evaluated in combination with prednisone and abiraterone in an ongoing phase III (IPATential150) study for the treatment of metastatic castration-resistant prostate cancer (mCRPC) patients.[5] The primary analysis results from the IPATential150 study showed that ipatasertib in combination with prednisone and abiraterone improved radiographic progression-free survival in mCRPC patients with PTEN-loss tumors compared to placebo plus prednisone and abiraterone. Safety results showed that the overall incidences of hyperglycemia were higher in the ipatasertib-prednisone-abiraterone arm compared to the placebo-prednisone-abiraterone arm; placebo was included as a matching pill for ipatasertib to preserve blinding within this study. The frequency for Grade 3–5 hyperglycemia was 14.2% ($n = 78$ patients) in the ipatasertib-prednisone-abiraterone arm compared to placebo arm which was 1.3% ($n = 7$ patients).[5] Incidences of hyperglycemia were also higher in the IPATential150 study when compared to ipatasertib in combination with paclitaxel in breast cancer indication.[6–8]

Hyperglycemia is an on-target effect of AKT inhibition. AKT pathway has been reported to play an important role in glucose homeostasis and mediates the metabolic effects of insulin by increasing the uptake of glucose within the cells and by decreasing hepatic gluconeogenesis.[9] As ipatasertib inhibits AKT, it likely imparts a reverse effect on the insulin-stimulated glucose pathway, which can eventually lead to increased concentrations of glucose in the body. As the mechanism of action suggests, the increase in glucose levels following ipatasertib administration are usually transient and tend to return to baseline within 6 h, likely as ipatasertib exposure decreases.[2] Within this study, 400 mg q.d. ipatasertib was administered alone, ipatasertib was administered in combination with prednisone 5 mg b.i.d., and ipatasertib was administered in combination with prednisone 5 mg b.i.d. and abiraterone 1000 mg q.d. separately as a morning or evening dose. Prednisone, a glucocorticoid, has been shown to promote gluconeogenesis which can result in increased glucose concentrations

in the body.[10] In the current study, we aimed to investigate the cause of increase in incidences of hyperglycemia by sequential addition of ipatasertib, prednisone, and abiraterone to investigate effect on glucose as well as potential for drug–drug interaction (DDI). Ipatasertib is a CYP3A4 and P-gp substrate.[11] M1 is the major metabolite formed which is pharmacologically active but is 3- to 5-fold less potent than ipatasertib at AKT inhibition. Both ipatasertib and M1 exhibit low human plasma protein binding. Increased ipatasertib exposures have been observed in combination with abiraterone[12] and given that the AKT inhibition may be exposure dependent, it is hypothesized that hyperglycemia could be higher with such an increase in ipatasertib exposure.

We also aimed to investigate a potential risk mitigation approach of restriction of food intake after dosing. Food intake is known to increase blood glucose levels and may potentiate the overall glucose increase, as ipatasertib is typically administered after overnight fasting where the meal is taken by the patients 1–2 h post-ipatasertib dose administration. Since nighttime is naturally amenable to overnight fast, we investigated this by dosing ipatasertib and abiraterone in the evening after a meal instead of a morning dose followed by a meal. A wearable continuous glucose monitor (CGM) was employed to track glucose values closely in real time.

The overall goal of this study was thus to evaluate:

1. Glucose changes when ipatasertib is administered alone versus in combination with prednisone versus in combination with prednisone and abiraterone.
2. Ipatasertib exposures in presence and absence of abiraterone.
3. Correlation between ipatasertib exposures and glucose levels.
4. Whether evening dosing of ipatasertib post-meal provides a better alternative at managing glucose levels.

METHODS

Clinical study

This was an open-label, single-arm, single-sequence, safety cohort crossover study conducted to evaluate ipatasertib and abiraterone DDI and to characterize glucose changes that are associated with the different treatment periods: ipatasertib monotherapy, ipatasertib plus prednisone combination, ipatasertib plus prednisone plus abiraterone combination (morning dose), and ipatasertib plus prednisone plus abiraterone combination (evening dose). Figure 1 illustrates the clinical study design. A total of 25 mCRPC male patients were enrolled in this study and a DexCom G6 CGM wearable device was used during the first cycle (from Cycle 1 Day −1 to Cycle 2 Day 1) to capture the dynamic glucose changes over the four treatment periods. Cycle 1 consisted of 25 days and subsequent cycles consisted of 28 days. Ipatasertib 400 mg q.d. was administered as a morning dose from Cycle 1 Days 1–18 where the drug was taken at least 1 h prior to the first meal of the day. For Cycle 1 Days 19–25, ipatasertib was taken in the evening at least 2 h after the last meal of the day, and patients were asked to avoid eating overnight (Figure S1). Prednisone, 5 mg b.i.d. was started in the evening from Cycle 1 Day 8. Abiraterone, 1000 mg q.d. was started from Cycle 1 Day 12 where both
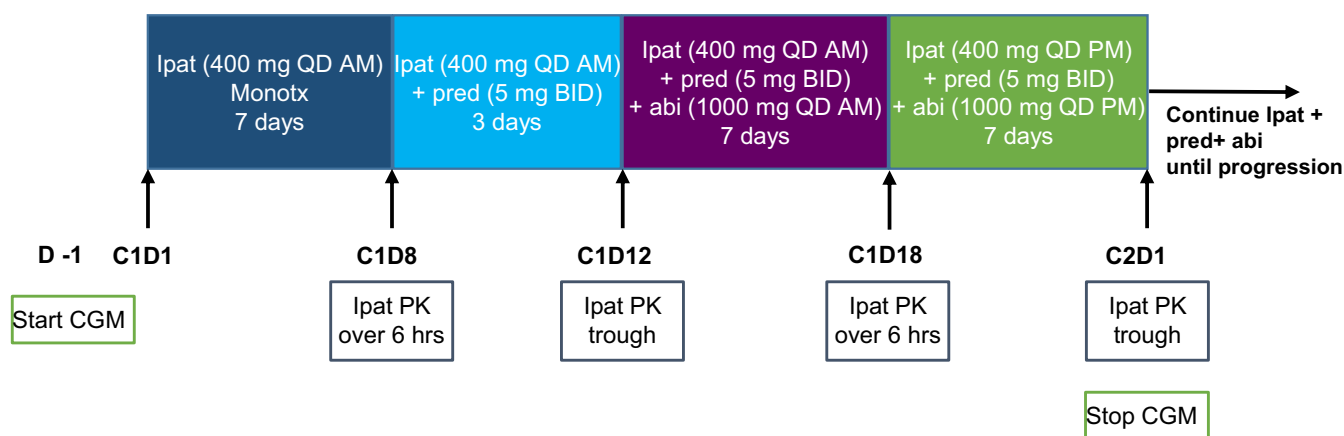
ipat=ipatasertib; QD= once a day; monotx=monotherapy; PK=pharmacokinetic; pred=prednisone/prednisolone; Abi=abiraterone; BID=twice a day; C=Cycle; CGM=continuous glucose monitoring; D=Day(s)

FIGURE 1 Schematic representation of the study design.

ipatasertib and abiraterone were taken at approximately the same time. The crossover study design was enabled to reduce the carryover effects of the previous treatment period. Ipatasertib reaches steady state within 7 days of dosing,[2] so ipatasertib pharmacokinetics (PK) and glucose levels were evaluated at Cycle 1 Day 8 at steady-state levels. Prednisone is a fast-acting glucocorticoid, and as abiraterone reaches steady state after 7 days of dosing, ipatasertib-prednisone combination was administered for three consecutive days and ipatasertib-prednisone-abiraterone combination for seven consecutive days for both first morning and later as an evening dose in order to evaluate the effect of the combination regimens on PK and glucose at steady-state levels.

Blood sample collection for PK characterization of ipatasertib and its 3–5-fold less active M1 (G-037720) metabolite was done on Cycle 1 Day 8, Cycle 1 Day 12, and Cycle 1 Day 18 where 0- to 6-h samples were collected on Cycle 1 Days 8 and 18 to compare ipatasertib exposures with/without prednisone and abiraterone. Trough samples were collected on Cycle 1 Day 12 to compare the effect of prednisone on ipatasertib PK.

Continuous glucose monitoring data were collected from Cycle 1 Day −1 when the CGM device was applied.

The patients were blinded to the glucose measurement and glucose data were collected from Cycle 1 Day −1 to Cycle 2 Day 1. All routine safety monitoring and management related to hyperglycemia were conducted based on the fasting blood glucose that was drawn in the clinic.

This study was conducted in full conformance with the International Council for Harmonisation (ICH) E6 guideline for Good Clinical Practice and the principles of the Declaration of Helsinki, or the applicable laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the individual. The study complied with the requirements of the ICH E2A guideline (Clinical Safety Data Management: Definitions and Standards for Expedited Reporting). This study was conducted in the United States or under a US Investigational New Drug (IND) Application and it complied with US FDA regulations and applicable local, state, and federal laws. The study was conducted in the European Union or European Economic Area and it complied with the EU Clinical Trial Directive (2001/20/EC) and applicable local, regional, and national laws.
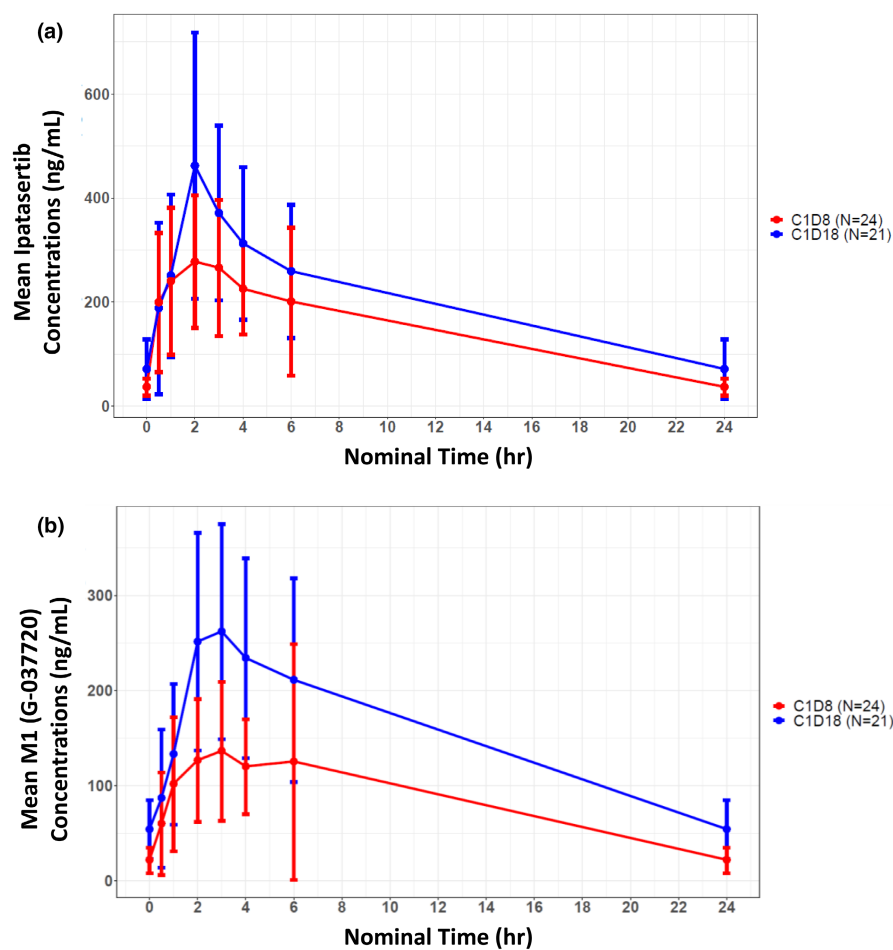

FIGURE 2 Mean ± standard deviation concentration–time profiles for (a) ipatasertib and (b) M1 (G-037720) plasma after the administration of ipatasertib in absence (C1D8) and presence of abiraterone (C1D18).

Glucose analysis

Glucose data in this study was collected using the commercial Dexcom G6 continuous glucose-monitoring wearable device. The limit of quantitation for the CGM device was as per the manufacturer's information. Based on the published article[13] which describes the use of continuous glucose-monitoring four key parameters, average glucose over 24 h, peak glucose over 24 h, % time in range (70–180 mg/dl) over 24 h, and % time above range >180 mg/dl over 24 h were evaluated across the four treatment periods for glucose comparison. Glucose levels for ipatasertib monotherapy were evaluated from Cycle 1 Day 7 to Cycle 1 Day 8. Glucose levels for ipatasertib in combination with prednisone were evaluated from Cycle 1 Day 11 to Cycle 1 Day 12. Glucose levels were evaluated on Cycle 1 Day 17 to Cycle 1 Day 18 when ipatasertib in combination with prednisone and abiraterone was administered as a morning dose and from Cycle 1 Day 24 to Cycle 1 Day 25 when ipatasertib was administered as an evening dose in combination with prednisone and abiraterone. All the 24 h evaluations mentioned above were done from the first until the next dose of ipatasertib administration. Baseline glucose levels (24 h prior to ipatasertib monotherapy administration [i.e., Cycle 1 Day 1]) were collected for each patient that was used for benchmarking comparisons across the different treatment periods.

PK analysis

Plasma samples were evaluated for ipatasertib and M1 metabolite using a validated liquid chromatography tandem mass spectrometry assay.[11] The lower and upper limit of quantitation for ipatasertib was 0.500 and 400 ng/ml, respectively. The lower and upper limit of quantitation for M1 metabolite was 0.500 and 400 ng/ml, respectively. Stable labeled internal standards were used for both analytes. PK noncompartmental analysis was performed using commercial software Phoenix WinNonlin (Certara USA, Inc., version 8.1). PK samples at steady state were collected at pre-dose, 0.5, 1, 2, 3, 4, and 6 h post-dose on Cycle 1 Day 8 and Cycle 1 Day 18 to evaluate ipatasertib and M1 exposures in the presence and absence of abiraterone. Area under the curve $(AUC)_{0-24h,ss}$ exposures were extrapolated using the pre-dose concentrations as 24-h time point. A minimum of three data points were used for both PK timepoints (i.e., Cycle 1 Day 8 and Cycle 1 Day 18) for the determination of the beta-phase.

Statistical analysis

Descriptive statistics (mean, standard deviation, median, minimum, maximum, geometric mean, and geometric coefficient of variation) were calculated for all PK parameters for ipatasertib and M1 metabolite. For T_{max} estimation only mean, median, minimum, and maximum were evaluated. PK parameters ($AUC_{0-t,ss}$ and $C_{max,ss}$) were compared between Cycle 1 Day 8 (ipatasertib monotherapy, as the reference treatment) and Cycle 1 Day 18 (ipatasertib in combination with prednisone and abiraterone, as the test treatment) by calculating geometric mean ratios and 90% confidence intervals (90% CIs) to evaluate the effect of abiraterone on the PK of ipatasertib and M1 metabolite. Glucose parameters (peak glucose over 24 h and average glucose over 24 h) were compared between the different treatment periods by calculating geometric mean ratios and 95% CIs. The statistical significance was evaluated using the analysis of variance (ANOVA) method.

In order to evaluate the pharmacokinetic–pharmacodynamic (PK–PD) relationship, different models including linear regression analysis, nonlinear regression analysis, and linear mixed-effect modeling was performed using ipatasertib PK (C_{max}, $AUC_{0-24h,ss}$) exposures and glucose parameters (peak glucose over 24 h and average glucose over 24 h). The linear mixed-effect modeling was performed using SAS version 9.4 on log-transformed primary PK parameters. Linear mixed-effect model was conducted to account for intra- and interindividual variability and to allow the pooling of the two treatment groups: ipatasertib monotherapy (i.e., C1D8 timepoint) and ipatasertib-prednisone-abiraterone (i.e., C1D18 timepoint) in order to evaluate the effect of ipatasertib exposures on glucose changes.

RESULTS

Effect of ipatasertib on glucose levels

Four glucose parameters: peak glucose over 24 h, average glucose over 24 h, % time in range (70–180 mg/dl) over 24 h, and % time above range (>180 mg/dl) over 24 h were evaluated using the CGM data following administration of ipatasertib monotherapy, ipatasertib in combination with prednisone, and ipatasertib in combination with prednisone and abiraterone when administered separately as a morning and evening dose.

Peak glucose analysis over 24 h showed a marked increase in peak glucose levels over the four different treatment periods when compared to baseline (Figure 3, Table 1). The peak glucose geometric mean ratio (95% CI) compared to baseline was 1.28 (1.13, 1.53) for ipatasertib monotherapy, 1.27 (1.13, 1.48) for ipatasertib and prednisone combination, 1.56 (1.38, 1.85) for ipatasertib in combination with prednisone and abiraterone
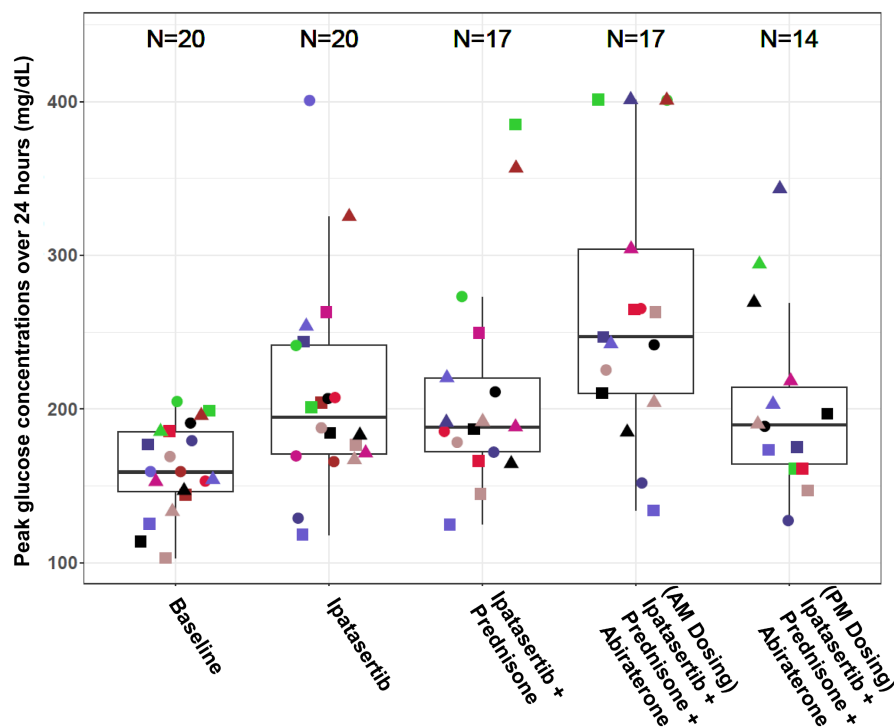
FIGURE 3 Summary of peak glucose levels over 24 h across the four different treatment periods.

TABLE 1 Geometric mean ratios (95% confidence intervals) for peak glucose over 24 h and average glucose over 24 h for the four different treatment periods when compared to baseline

Treatment arms	Peak glucose over 24 h		Average glucose over 24 h	
	GMR (95% CI)	*p* Value	GMR (95% CI)	*p* Value
Ipatasertib monotherapy	1.28 (1.13, 1.53)	0.0044	1.18 (1.07, 1.34)	0.0128
Ipatasertib + prednisone	1.27 (1.13, 1.48)	0.00638	1.17 (1.06, 1.32)	0.0187
Ipatasertib + prednisone + abiraterone (morning dose)	1.56 (1.38, 1.85)	<0.001	1.31 (1.14, 1.56)	0.00217
Ipatasertib + prednisone + abiraterone (evening dose)	1.25 (1.1, 1.47)	0.0107	1.26 (1.09, 1.49)	0.00547

Abbreviations: CI, confidence interval; GMR, geometric mean ratio.

when administered as a morning dose, and 1.25 (1.10, 1.47) for ipatasertib in combination with prednisone and abiraterone when administered as an evening dose. Ipatasertib in combination with prednisone did not show any change in peak glucose levels compared to ipatasertib monotherapy. Peak glucose levels when ipatasertib was administered in the evening in combination with prednisone and abiraterone were similar to that of ipatasertib monotherapy. A statistically significant reduction was observed in peak glucose when ipatasertib was administered in combination with prednisone and abiraterone in the evening compared to the morning (*p* value = 0.0276).

Similar to peak glucose levels, average glucose over 24 h was increased during the four different treatment periods compared to baseline (Figure 4). The average glucose geometric mean ratio (95% CI) when compared

to baseline was 1.18 (1.07, 1.34) for ipatasertib monotherapy, 1.17 (1.06. 1.32) for ipatasertib and prednisone combination, 1.31 (1.14, 1.56) for ipatasertib in combination with prednisone and abiraterone when administered as a morning dose, and 1.26 (1.09, 1.49) for ipatasertib in combination with prednisone and abiraterone when administered as an evening dose. No changes in average glucose levels were observed between ipatasertib monotherapy and ipatasertib when administered in combination with prednisone. Average glucose levels were not statistically significant (*p* value = 0.454) when ipatasertib was administered as a morning versus an evening dose in combination with prednisone and abiraterone.

Time-in-range (70–180 mg/dl) and time above range >180 mg/dl was evaluated to study the overall glucose changes during the four different treatment periods.

FIGURE 4 Summary of average glucose over 24 h across the four different treatment periods.
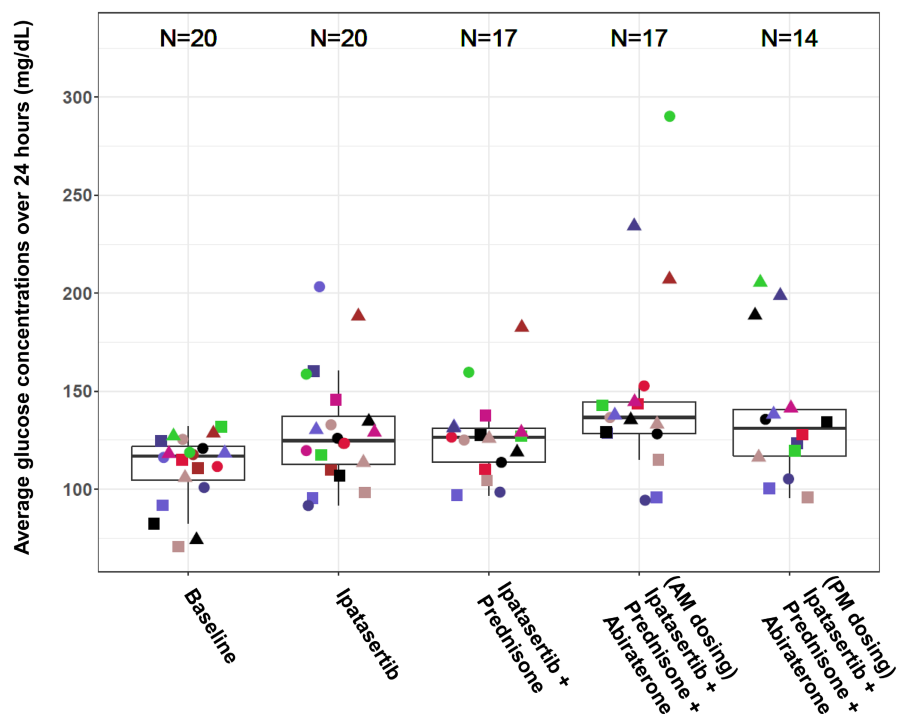
Time-in-range and time above range values across the treatment periods are reported as percentages. The mean % time-in-range (indicated as "+" within Figure 5) was similar across baseline (85.29%), ipatasertib monotherapy (87.33%), and ipatasertib and prednisone combination (90.82%). The % time in range reduced to 75.77% when ipatasertib was administered as a morning dose in combination with prednisone and abiraterone. When this combination was switched to an evening dose, the % time in range improved from 75.77% to 87.25%. The % time above range analysis (i.e., >180 mg/dl) shows an increase in the % time the subject spends above the normal glucose levels when ipatasertib is administered. The mean % time above range >180 mg/dl increased from 2.21% at baseline to 10.04% after ipatasertib administration. There was no difference observed between ipatasertib monotherapy and ipatasertib-prednisone treatment. The mean % time above range increased to 19.03% when ipatasertib was administered as a morning dose in combination with prednisone and abiraterone. When this combination was switched to an evening dose, the mean % time above range was reduced to 11.41%, values of which are comparable to ipatasertib monotherapy treatment period.

Ipatasertib and M1 PK in the absence and presence of abiraterone

Ipatasertib $C_{max,ss}$ and $AUC_{0-24h,ss}$ exposures increased in the presence of abiraterone (Figure 2, Table 2). Based on the statistical analysis conducted to evaluate the effect
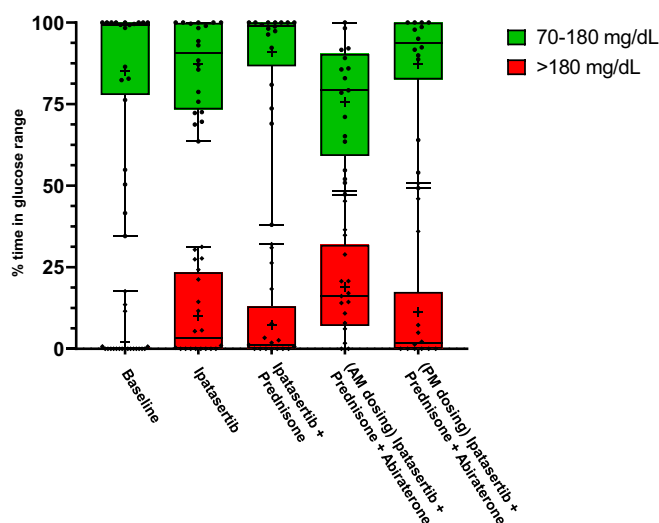

FIGURE 5 Box plot summarizing percentage time in glucose range for patients across the four different treatment periods. The '+' sign is representative of the arithmetic mean values for all patients within the glucose range and treatment period.

of abiraterone on ipatasertib PK, $C_{max,ss}$ and $AUC_{0-24h,ss}$ geometric mean ratios (90% CIs) of approximately 1.46 (1.33–1.75) and 1.47 (1.32–1.82), respectively, were observed. M1 (G-037720) metabolite $C_{max,ss}$ and $AUC_{0-24h,ss}$ exposures also increased when ipatasertib was administered with abiraterone (Figure 2b, Table 2). M1 geometric mean ratios (90% CIs) were approximately 2.11 (1.97–2.35) and 2.20 (2.03–2.52) for $C_{max,ss}$ and $AUC_{0-24h,ss}$, respectively.

TABLE 2 Summary of ipatasertib and M1 (G-037720) pharmacokinetics in absence and presence of abiraterone

Analyte	Treatment period	N	$C_{max,ss}$ (ng/ml) Geomean (geo%CV)	$C_{max}R$ (C1D18/C1D8) Geomean (90% CI)[a]	$AUC_{0-24,ss}$ (ng×h/ml) Geomean (geo%CV)	AUCR (C1D18/C1D8) Geomean (90% CI)[a]	M/P ($AUC_{0-24,ss}$ M1/ipat)
Ipatasertib	C1D8 (ipat alone,ss)	23	315 (46.2%)	1.46 (1.33–1.75)	2580 (53.4%)	1.47 (1.32–1.82)	–
	C1D18 (ipat + abi,ss)	21	467 (44.2%)		3920 (50.5%)		–
M1 (G-037720)	C1D8 (ipat alone,ss)	23	145 (58.10%)	2.11 (1.97–2.35)	1360 (55.4%)	2.20 (2.03–2.52)	0.527 (38.1%)
	C1D18 (ipat + abi,ss)	21	281 (37.90%)		2870 (55.2%)		0.732 (30.0%)

Abbreviations: abi, abiraterone; $AUC_{0-24,ss}$, area under the curve from 0 to 24 h at steady state; AUCR, geometric mean ratio of $AUC_{0-24,ss}$; $C_{max,ss}$, maximal plasma concentration at steady state; $C_{max}R$, geometric mean ratio of $C_{max,ss}$; ipat, ipatasertib; M/P, metabolite to parent ratio.

[a]$N = 20$.

Exposure–response analysis

In order to understand the relationship between ipatasertib treatment and glucose changes, exposure–response analysis was conducted using the PK exposure ($C_{max,ss}$ and $AUC_{0-24h,ss}$) and glucose data (peak glucose over 24 h and average glucose over 24 h) from two different treatment periods: ipatasertib monotherapy (Cycle 1 Day 8) and ipatasertib-prednisone-abiraterone combination (Cycle 1 Day 18). Good correlation was observed between ipatasertib $C_{max,ss}$ concentrations and peak glucose levels ($p < 0.001$) and ipatasertib $C_{max,ss}$ concentrations and average glucose levels ($p = 0.001$) (Figure 6). Similar correlations were observed between ipatasertib $AUC_{0-24h,ss}$ and peak and average glucose levels (data not shown). These results indicate that increase in ipatasertib concentrations is correlated with increase in overall glucose profiles.

DISCUSSION

Glucose monitoring has been conventionally carried out using either a fingerstick or venipuncture in laboratory glucose measurement, both of which only measure glucose levels at a single moment in time. Glucose changes are more dynamic in nature, and can vary based on the meal intake or drug administration.[14] The goal of this study was thus to capture the real-time changes in the glucose values post-ipatasertib monotherapy or in combination with prednisone (glucocorticosteroid) and abiraterone (AR inhibitor). This crossover study was conducted such that potential carryover effects of each of the treatments into the next treatment period was minimized and glucose levels were evaluated at steady state for each of the four different treatment periods. In this study, the Dexcom G6 CGM

device was used which measures the glucose levels within the interstitial fluid. Blood glucose levels measured by venipuncture in this study demonstrated good correlation with interstitial glucose levels measured via the CGM device (Figure S2). The use of a CGM wearable device in this study allows us to discern the changes in glucose levels when ipatasertib is administered under the four different treatment periods.

In this study, ipatasertib was administered in combination with prednisone, a glucocorticoid that has been reported to increase hyperglycemia incidences through the regulation of glucose homeostasis.[10] A low dose of prednisone was administered (i.e., 5 mg b.i.d.) in this study compared to the typical dose associated with hyperglycemia (i.e., 25 mg b.i.d.). The purpose of administering this low-dose prednisone was to serve as a glucocorticoid replacement therapy when administered in combination with abiraterone.[15] The data generated in this study showed that a low dose of glucocorticoid did not result in an increase in glucose levels when administered in combination with ipatasertib (Figures 3–5). All the glucose parameters, namely peak glucose over 24 h, average glucose over 24 h, % time in range (70–180 mg/dl), and above range (>180 mg/dl) that were evaluated within this study do not show any change in glucose profiles for ipatasertib plus prednisone compared to ipatasertib monotherapy.

Higher exposures of ipatasertib and M1 metabolite have been observed when coadministered with abiraterone.[12] Ipatasertib is not expected to affect abiraterone exposures, and data from other clinical studies (data not presented) show comparable exposures for abiraterone when administered in combination with ipatasertib. In this study, potential DDI between ipatasertib and abiraterone was evaluated in a single crossover study design. Ipatasertib and M1 metabolite $AUC_{0-24h,ss}$ exposures were

FIGURE 6 Correlation plots between ipatasertib exposure and glucose levels.
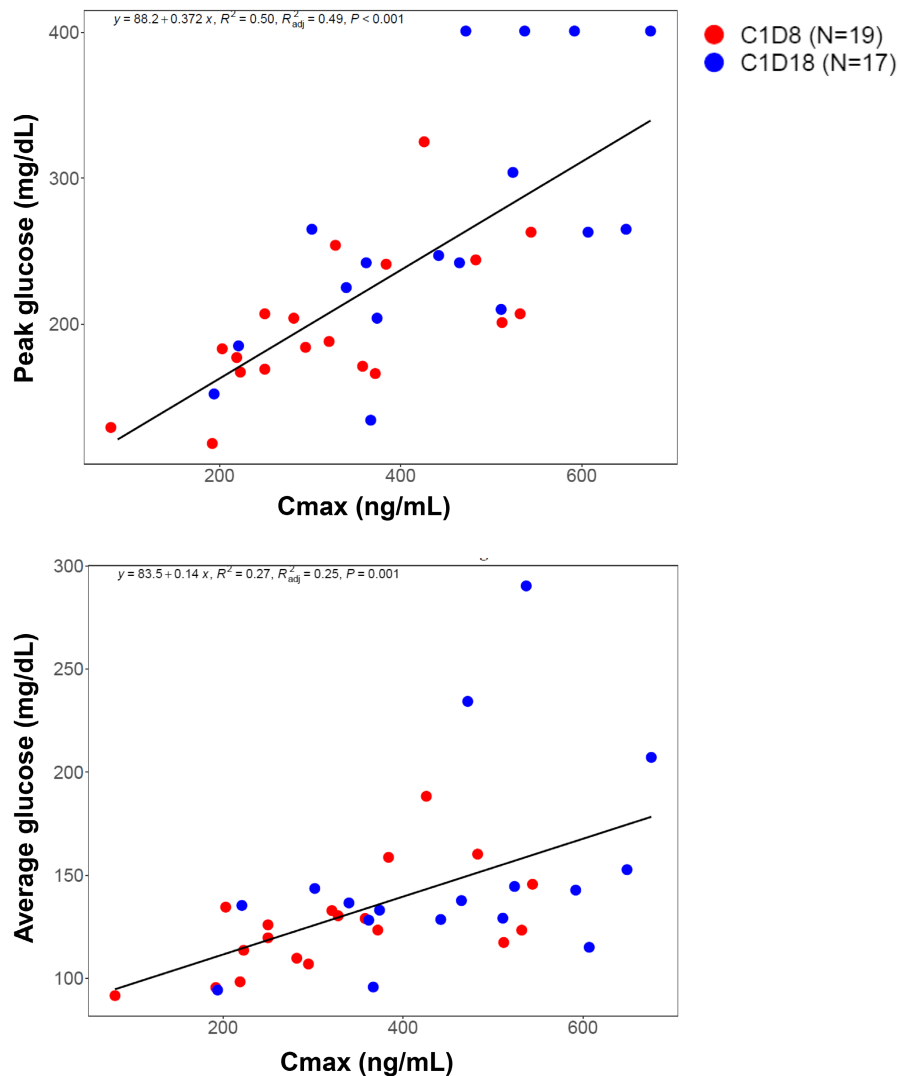
increased by ~1.5- and 2.2-fold, respectively, when ipatasertib was coadministered with abiraterone. Overall, the metabolite:parent ratio for ipatasertib when administered alone was 0.527; however, in the presence of abiraterone it has been observed to be higher (0.732). Since M1 is 3–5-fold less active at AKT inhibition than ipatasertib, M1 is considered to have no meaningful impact on efficacy as well as on-target safety event (i.e., glucose changes). The mechanism behind this DDI is still not completely understood as both ipatasertib and M1 are metabolized primarily by CYP3A4. In clinical DDI studies, coadministration of ipatasertib with enzalutamide, a strong CYP3A inducer, decreased ipatasertib exposure by 50% and increased M1 exposure by 15%. In another study, ipatasertib when coadministered with itraconazole, strong CYP3A inhibitor increased ipatasertib AUC exposure by ~5-fold and reduced the M1 AUC exposures by ~68%.[11] Unlike what was observed in the ipatasertib-itraconazole DDI study, ipatasertib and M1 exposures in the presence of abiraterone follows opposite trends. Ipatasertib $AUC_{0-24h,ss}$ exposures were increased by ~1.5-fold and M1 $AUC_{0-24h,ss}$ exposures

were increased by ~2.2-fold, which indicates the role of other CYP isoforms and/or drug transporters. The mechanistic understanding of this DDI was beyond the scope of this study.

Ipatasertib, when administered as a morning dose in combination with prednisone and abiraterone, showed statistically significant increases in peak and average glucose profiles compared to baseline, ipatasertib monotherapy, and ipatasertib-prednisone combination (Figures 3–5, Table 1). Based on the exposure–response linear regression analysis and nonlinear regression analysis (not shown) that was conducted, it was observed that the increase in glucose levels strongly correlated with the overall increase in ipatasertib exposures postmorning dose administration of ipatasertib-prednisone-abiraterone combination. This exposure–response analysis partly explains the reason behind the increased incidences of hyperglycemia when ipatasertib is administered in combination with prednisone and abiraterone. Unlike ipatasertib and prednisone, abiraterone is not reported to have a major impact on the glucose pathway

and the overall incidences of hyperglycemia were comparable between abiraterone-prednisone and placebo-prednisone.[16] Lower incidences of hyperglycemia may be expected when combined with other chemotherapeutic agents where DDI does not result in increased exposures of ipatasertib.[6–8,12]

Within previously conducted ipatasertib clinical trials it has been observed that there is a delayed effect in the time it takes to achieve the peak glucose levels post-ipatasertib dose administration, which is typically 4–6 h post-ipatasertib dose.[2] This delayed effect is partly because of the food effect as patients are taking their first meal of the day at least 1–2 h post-ipatasertib dose administration. In order to mitigate the cumulative food and drug effect, an option of evening dosing was evaluated. For evening dosing of ipatasertib, patients took the medication at least 2 h after the last meal of the day and were asked to avoid eating overnight (Figure S1). As patients took ipatasertib after the evening meal, postprandial glucose peak was not observed (Figure S3). This is reflected in the results from the peak glucose parameter (Figure 3). The peak glucose GMR (95% CI) for the ipatasertib-prednisone-abiraterone combination when administered as an evening dose compared to a morning dose reduced from 1.56 (1.38, 1.85) to 1.25 (1.1, 1.47). A similar trend was observed in the % time in range analysis, where the patients spent less % time in target range (70–180 mg/dl) and more time above target range (i.e., >180 mg/dl) when the ipatasertib-prednisone-abiraterone combination was administered in the morning compared to the evening (Figure 5). There were few study limitations encountered during the glucose analysis (e.g., not all of the patient CGM data were available for analysis). Some of the CGM patient data were lost due to device failure or due to device data transfer issues, which resulted in less patient data for the later time points. In addition, the CGM device has a ULOQ of 400 mg/dl because of which glucose values above the upper limit of quantification (ULOQ) were not available. However, for the purpose of evaluating overall glucose trends and exposure–response relationships, this was not considered to be a limitation.

This study was conducted as a signal-seeking study to understand and capture the glucose dynamics for ipatasertib in combination with prednisone and abiraterone and was not powered for statistical significance. In this study, we focused on evaluating the influence of morning versus evening dose on glucose modulation from primarily a food intake timing perspective. Food was expected to have a bigger impact on glucose level or PK/PD relationships[17] compared to any potential effect of circadian cycle. As food can cause large postprandial glucose peaks, we hypothesized that change in the timing of food intake

with respect to the timing of ipatasertib dose administration can help mitigate the risk of increase in blood glucose levels. As described in the Methods section, upon the administration of ipatasertib-prednisone-abiraterone combination in the evening, patients are advised to not partake in meals through the night, whereas patients only need to restrict food consumption for 2 h after the morning dose administration of the same. Based on the results, although the effect on glucose between morning and evening dosing is modest, the change was fairly consistent across patients and therefore could be a way to prevent large spikes in blood glucose and provide a promising approach for mitigating long-term risks. However, additional studies are needed to evaluate if sustained moderation of glucose peaks by employing post-meal evening dosing can translate into overall reduction of incidences of Grade 2+ hyperglycemia as compared to the typical morning dosing.

In conclusion, this is the first clinical study to evaluate the real-time glucose changes between a morning and an evening dose when ipatasertib is administered in combination with prednisone and abiraterone. The results from this study suggest that offering ipatasertib as an evening dose in combination with prednisone and abiraterone followed by overnight fasting may offer a way to mitigate risk of hyperglycemia.

AUTHOR CONTRIBUTIONS
D.S.S., P.A., D.R.M., and R.S. wrote the manuscript. J.R., G.R., and R.S. designed the study. D.S.S., P.A., K.-C.H., H.H., J.D.G., G.R., and R.S. performed the research. D.S.S., P.A., D.R.M., and R.S. analyzed the data.

CONFLICT OF INTEREST
All authors are past or present employees of Genentech or Roche.

DATA AVAILABILITY STATEMENT
Qualified researchers may request access to individual patient-level data through the clinical study data request

platform (https://vivli.org/). Further details on Roche's criteria for eligible studies are available here (https://vivli.org/members/ourmembers/). For further details on Roche's Global Policy on the Sharing of Clinical Information and how to request access to related clinical study documents see https://www.roche.com/research_and_development/who_we_are_how_we_work/clinical_trials/our_commitment_to_data_sharing.html.

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SUPPORTING INFORMATION

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