Abemaciclib inhibits renal tubular secretion without changing glomerular filtration rate.

Abemaciclib, an inhibitor of cyclin dependent kinases 4 and 6, is indicated for metastatic breast cancer treatment. Reversible increases in serum creatinine levels of ~15–40% over baseline have been observed following abemaciclib dosing. This study assessed the in vitro and clinical inhibition of renal transporters by abemaciclib and its metabolites using metformin (a clinically relevant transporter substrate), in a clinical study that quantified glomerular filtration and iohexol clearance. In vitro, abemaciclib inhibited metformin uptake by organic cation transporter 2, multidrug and toxin extrusion (MATE)1, and MATE2-K transporters with a half-maximal inhibitory concentration of 0.4–3.8 μM. Clinically, abemaciclib significantly increased metformin exposure but did not significantly affect measured glomerular filtration rate, serum neutrophil gelatinase-associated lipocalin (NGAL), serum cystatin-C, or the urinary markers of kidney tubular injury, NGAL and kidney injury molecule-1.

Study Highlights

**WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?**
- Multiple drugs decrease estimated glomerular filtration rate (eGFR) via inhibition of renal transporters without directly affecting renal function. Clinical studies of abemaciclib revealed treatment-associated increases in serum creatinine (SCr) and decreases in eGFR.

**WHAT QUESTION DID THIS STUDY ADDRESS?**
- Does abemaciclib cause increases in SCr due to inhibition of renal transporters or because of alterations to GFR?

**WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?**
- Abemaciclib inhibits organic cation transporter 2, multidrug and toxin extrusion (MATE)1, and MATE2-K transporters in vitro and significantly decreases renal clearance of metformin, a transporter substrate. Abemaciclib did not significantly increase measured GFR or acute renal damage biomarkers, suggesting that observed increases in SCr are due to inhibition of proximal tubule secretory transporters.

**HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?**
- These findings indicate that abemaciclib does not seem to affect renal function: alternative renal function assessment methods may be required in patients taking abemaciclib when increases in creatinine are reported and clinicians are concerned about impairment of renal function. The design allows transporter inhibition and effects upon GFR to be evaluated in the same study.

Abemaciclib is an orally administered small molecule that is a potent and selective inhibitor of cyclin-dependent kinases (CDKs) 4 and 6.\(^1\) Inhibition of CDK4 and CDK6 prevents cell cycle progression through the G1 restriction point, which controls entry into S phase, thus arresting tumor growth.\(^2\) Abemaciclib is indicated for the treatment of metastatic breast cancer.

In clinical studies of patients with cancer and healthy subjects, reversible increases in serum creatinine (SCr) levels of ~15–40% over baseline were measured following dosing with abemaciclib.\(^3\)\(^,\)\(^5\) Creatinine, an endogenous product of creatine phosphate metabolism in skeletal muscle, is the most widely used marker to estimate glomerular filtration rate (eGFR) in the clinical setting. Although creatinine is primarily filtered in the kidneys,\(^4\)\(^,\)\(^5\) active tubular secretion accounts for ~10–40% of creatinine clearance.\(^6\)\(^–\)\(^9\) Thus, the glomerular filtration rate (GFR) calculated using SCr levels could be an overestimate.

Active tubular secretion of creatinine is mediated by multiple solute carrier (SLC) transporters in the kidney, including organic cation transporter 2 (OCT2: SLC22A2), multidrug and toxin extrusion protein (MATE) 1 (SLC47A1), and MATE2-K (SLC47A2).\(^5\)\(^,\)\(^10\)\(^,\)\(^11\) OCT2 is expressed on the basolateral membrane of proximal tubule cells and mediates uptake of organic cations, such as creatinine and metformin, from blood into the cells by facilitated diffusion;\(^12\) however, MATE1 and MATE2-K are expressed on the apical membrane of proximal tubule cells and are responsible for proton-coupled efflux of drugs and endogenous compounds from cells to urine.\(^13\) Inhibition of OCT2 and/or MATEs can, therefore, lead to a decrease in creatinine clearance.
and a corresponding increase in SCr due to inhibition of its tubular secretion. These changes can occur without clinically meaningful alterations in renal function or impact on measured GFR (mGFR).9,10,13

The in vitro assessment of OCT2 and/or MATE inhibition is important in evaluating potential for drug–drug interactions (DDIs) at these transporters and for many drugs recognized as having inhibitory potential.14 A number of marketed drugs cause elevations in SCr by inhibition of these renal transporters.15,16 Early assessment of the clinical inhibition of renal transporters may be prudent if transporter inhibition has been identified in vitro or if increases in SCr concentrations have been identified during preclinical development, or first-in-human clinical trials.

A widely used drug, metformin, is excreted unchanged in urine, principally via active tubular secretion in the kidneys17,18 by OCT2-mediated uptake followed by efflux via MATEs. It is well documented that concomitant administration of metformin with MATE and/or OCT2 inhibitors, such as pyrimethamine, cimetidine, or dolutegravir, changes the pharmacokinetics (PKs) of metformin.18–21

In the past decade, alternative markers for assessing GFR and renal function have been identified, including other endogenous substances, such as cystatin-C, which unlike SCr, is not subject to active secretion and not affected by changes in diet or muscle mass.22 Techniques using clearance rates of freely filtered and non-metabolized exogenous compounds, such as iohexol, are also used to calculate absolute GFR and better estimate the actual rate of glomerular filtration.23 A range of biomarkers, including kidney injury molecule 1 (KIM-1) and neutrophil gelatinase-associated lipocalin (NGAL), have been shown to be promising markers of acute kidney injury compared to SCr.16,24–26

This study aimed to assess the in vitro and clinical inhibition of renal transporters by abemaciclib and its active metabolites, M2 and M20, using metformin as a clinically relevant competing transporter substrate. The effect of abemaciclib administration on metformin PK was examined using a clinical study design incorporating monitoring of renal filtration, by measuring iohexol clearance, to demonstrate that observed increases in creatinine concentrations and subsequent decreases in calculated creatinine clearance and eGFR were due to transporter inhibition and not changes in renal function.

RESULTS
In vitro analysis of transporter interactions
The inhibitory effects of abemaciclib and its two active metabolites, M2 and M20, on renal transport of metformin were assessed in vitro using transfected human embryonic kidney (HEK) cells expressing OCT2, MATE1, and MATE2-K. Abemaciclib, M2, and M20 inhibited OCT2, MATE1, or MATE2-K–mediated metformin uptake with half-maximal inhibitory concentration (IC50) values ranging from 0.4–3.8 μM (Table 1 and Figure 1). When the unbound peak plasma concentration (Cmax) to in vitro IC50 ratio (DDI index) for abemaciclib was combined with DDI indices of M2 and M20, the DDI indices of OCT2, MATE1, and MATE2-K were 0.03, 0.13, 0.06, respectively (Figure 1). The DDI index for MATE1 and MATE2-K exceeded the regulatory guidance threshold of 0.02 indicating the potential for a DDI at these transporters at clinically relevant concentrations.27,28

Clinical study
Demographics. Forty healthy subjects, 4 men and 36 women, between the ages of 23 and 69 years were enrolled in the study. The demographic and baseline characteristics of the subjects are shown in Table 1.

All subjects were randomly assigned to a dosing sequence and received at least one dose of study drug. Twenty-five subjects completed the study through to the follow-up visit (Figure S1).

One subject discontinued due to adverse events of elevated alkaline phosphatase, elevated alanine aminotransferase, elevated aspartate aminotransferase, and elevated gamma glutamyltransferase enzymes, considered to be related to study treatment beginning on day 15 of period 2 (14 days after receiving abemaciclib and metformin). Five subjects were lost to follow-up, and five subjects withdrew their consent for personal reasons. For the PK analysis, data were available from 30 subjects who received placebo and metformin, 32 subjects who received abemaciclib and metformin, 32 subjects who received placebo and iohexol, and 33 subjects who received abemaciclib and iohexol. Figure S1 summarizes subject disposition and data evaluable.
Effect of abemaciclib coadministration on metformin PKs. Coadministration of metformin with abemaciclib increased exposure to metformin (Figure 2), causing a statistically significant increase in metformin geometric least squares (LS) mean area under the concentration-time curve from zero to infinity (AUC0–∞) and Cmax, and a nonsignificant delay in time of maximum plasma concentration (Tmax; Table 2).

Statistically significant decreases in metformin renal clearance (CLR) and clearance of renal secretion (CLRS) were observed in the presence of abemaciclib (Figure 2 and Table 2).

Effect of abemaciclib on iohexol clearance and GFR. Coadministration of abemaciclib with iohexol did not affect iohexol PK, and there was notable overlap of the iohexol plasma concentration vs. time profiles in the presence of placebo or 400 mg abemaciclib (Figure 3). Iohexol clearance (mGFR) was equivalent following coadministration of iohexol with placebo or abemaciclib, with a ratio of geometric LS means of 0.982 (90% confidence interval (CI) 0.958–1.01, mean mGFR of 89.0 and 85.6 mL/minute for placebo and abemaciclib periods, respectively; Figure 3b).

Following both placebo and abemaciclib administration, SCr concentrations increased between 10 and 12 hours postdose (mean increases of 25–29 and 35.7–44.6 μmol/L, following placebo and abemaciclib administration, respectively), then decreased over time, with the maximum increase being higher following abemaciclib administration. Based on the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation using SCr, eGFR decreased in the presence of abemaciclib compared to placebo for the combination with metformin (65.4–57.2 mL/minute/1.73 m2) and iohexol (62.2 and 53.6 mL/minute/1.73 m2), respectively.

EGFR calculated using serum cystatin-C concentrations did not change between abemaciclib and placebo periods. At the time of maximal postdose creatinine concentrations, eGFR calculated using CKD-EPI showed decreases corresponding to higher creatinine values, whereas the eGFR calculated using cystatin-C at the same time point did not change. There were no trends in serum concentrations of cystatin-C following administration of placebo or the study drugs.

There were no trends in serum cystatin-C or NGAL indicative of renal injury following administration of placebo or abemaciclib with either metformin or iohexol (Figure 4). When the ratio of urine concentrations of KIM-1 and NGAL to urine creatinine concentrations were calculated, there seemed to be higher variability following dosing of abemaciclib with metformin but no other notable changes following dosing in any of the groups (Figure 5).

DISCUSSION
Abemaciclib administration has been associated with mild and variable but consistent elevations in SCr.14,15,29 Increased SCr can arise from a reduction in glomerular filtration, indicating damage to the nephron and associated reduction in renal function, or from inhibition of the active tubular secretion of creatinine. The active tubular secretion of creatinine, and other organic cations, is mediated at least in part by OCT2 at the
Abemaciclib and its major circulating metabolites would inhibit OCT2 and MATE1/2-K clinically. Inhibition constants (IC50) determined in vitro predicted that at therapeutic concentrations, abemaciclib and its major circulating metabolites would inhibit OCT2 and MATE1/2-K clinically.

This study was designed to clinically evaluate the hypothesis that mild, abemaciclib-induced elevations in SCr are a result of inhibition of active tubular secretion of creatinine and not a reduction in kidney function (as determined by mAUC0-∞). The statistical significance of this change was, however, not calculated.

The eGFR (as assessed by CKD-EPI) showed decreases following abemaciclib dosing, which were not reflected in mAUC0-∞ (as determined by iothalamate clearance), or mAUC0-∞ calculated from serum cystatin-C concentrations. No notable change in creatinine-normalized urinary concentrations of NGAL and KIM-1 (both biomarkers of renal injury) were observed. These data, combined with the observed changes in metformin T1/2, indicate that the changes in mAUC0-∞ observed in clinical studies of abemaciclib are due to reversible inhibition of renal tubular secretion of creatinine and are not the result of acute kidney injury.

The majority of commonly used estimates of GFR, such as those recommended by the Modification of Diet in Renal Disease study and CKD-EPI, rely on accurate steady-state measurement of SCr, which can introduce errors in estimates of renal function. With a crossover design, this study was able to combine a measurement of “true” GFR (as assessed by iothalamate clearance) alongside renal transporter inhibition (as assessed by metformin T1/2) to both quantify the inhibitory effect of an investigational drug and its impact on renal function in vivo.
The results described confirm that increases in SCr following abemaciclib administration are likely caused by inhibition of renal transporters and that abemaciclib does not affect renal function as assessed by mGFR, or increase in concentrations of urinary biomarkers of renal injury. The findings suggest that patients dosed with abemaciclib will experience a mild (~10–40%) reversible increase in SCr due to renal transport inhibition. However, it is possible that the observed increases in SCr following abemaciclib administration may be further elevated in subjects with already reduced renal function due to reduced renal reserve. When clinically indicated, alternative measurements of renal function, aside from creatinine-derived eGFR, should be used in patients taking abemaciclib to accurately assess renal function.

**METHODS**

**In vitro analysis of transporter interactions**

**Materials.** Abemaciclib and its metabolites M2 (LSN2839567) and M20 (LSN3106726) were synthesized by Eli Lilly (Indianapolis, IN). Radiolabeled (14C) metformin was purchased from American Radio labeled Chemicals (St. Louis, MO). All other chemicals were of analytical grade and purchased from commercial sources.

Stably transfected HEK cells expressing OCT2 or vector control (VC) were generated using previously described methods. Stably transfected HEK cells expressing OCT2 or vector control (VC) were purchased from Corning Life Sciences (Transpo cells, Bedford, MA).

**In vitro inhibition studies.** All inhibition studies were performed with (14C) metformin as a substrate for 2 minutes at 37°C in VC, OCT2, MATE1, and MATE2-K cells in 24-well BioCoat Poly-D-Lysine plates (Becton Dickinson, Franklin Lakes, NJ).

OCT2 and VC cells were washed and preincubated for 10 minutes in varying concentrations of inhibitor (0.00038–100 μM abemaciclib, M2, or M20, along with a positive control inhibitor, 100 μM imipramine) in duplicate wells per concentration. Experiments were initiated by the addition of 200 μL (14C) metformin (10 μM, 0.1 μCi/mL) in the presence of 0.00038–100 μM abemaciclib, M2, M20, imipramine, or absence of the inhibitor.

MATE1, MATE2-K, and VC cells were washed and preincubated in 40 mM ammonium chloride for 20 minutes. Inhibition studies were

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**Table 2 Summary of metformin pharmacokinetics**

| Parameter       | Treatment                                      | N  | Geometric LS means | Ratio of means | 90% CI       | P value |
|-----------------|------------------------------------------------|----|--------------------|----------------|--------------|---------|
| AUC$_{0-\infty}$ (ng.hour/mL) | Placebo + 1,000 mg metformin (reference)   | 30  | 12,245             | 1.37           | 1.28−1.46   | NA      |
|                 | 400 mg abemaciclib + 1,000 mg metformin (test) | 28  | 16,718             |                |              |         |
| C$_{\text{max}}$ (ng/mL)     | Placebo + 1,000 mg metformin (reference)   | 30  | 1,586              | 1.22           | 1.13−1.30   | NA      |
|                 | 400 mg abemaciclib + 1,000 mg metformin (test) | 28  | 1,930              |                |              |         |
| CL$_{\text{R}}$ (L/hour)     | Placebo + 1,000 mg metformin (reference)   | 30  | 21.5               | 0.550          | 0.504−0.600 | NA      |
|                 | 400 mg abemaciclib + 1,000 mg metformin (test) | 28  | 11.8               |                |              |         |
| CL$_{\text{RS}}$ (L/hour)    | Placebo + 1,000 mg metformin (reference)   | 29  | 16.0               | 0.381          | 0.323−0.450 | NA      |
|                 | 400 mg abemaciclib + 1,000 mg metformin (test) | 25  | 6.08               |                |              |         |
| T$_{\text{max}}$ (hour)      | Placebo + 1,000 mg metformin (reference)   | 24  | 3.03*              | 0.500*         | 0−0.983*    | 0.070   |
|                 | 400 mg abemaciclib + 1,000 mg metformin (test) | 24  | 3.76*              |                |              |         |

CL$_{\text{R}}$ was calculated using Eq. 3 and assumes no renal tubular reabsorption. AUC$_{0-\infty}$, area under the concentration-time curve from zero to infinity; CI, confidence interval; CL$_{\text{R}}$, renal clearance; CL$_{\text{RS}}$, clearance of renal secretion; C$_{\text{max}}$, peak plasma concentration; LS, least squares; NA, not applicable; T$_{\text{max}}$, time of maximum plasma concentration.

*Median. *Median of differences. *Approximate 90% CI.
performed in experiment solution containing 200 μL (14C) metformin (2 μM, 0.2 μCi/mL) in the presence of 0.00038−100 μM abemaciclib, M2, M20, 100 μM pyrimethamine, or absence of inhibitor in duplicate wells per concentration. The reaction was stopped by addition of ice cold Hanks balanced salt solution. Each well was then aspirated and washed once with ice-cold phosphate-buffered saline. Following the final aspiration, 400 μL 1% Triton X-100 in phosphate-buffered saline (v/v) was added per well for radiochemical detection and protein quantification.

Analysis of data for in vitro inhibition studies
For all inhibition studies, values were corrected for passive diffusion by subtracting the average velocity of control cells from the velocity at each concentration in transfected cells.

The inhibitor concentration resulting in 50% inhibition (IC50 value) was determined by nonlinear regression analysis using WinNonLin Professional, version 6.4 (Certara L.P., Princeton, NJ), using the following equation:

\[
\text{Percent of Control} = Y_{\min} + \frac{(Y_{\max} - Y_{\min})}{1 + \left(\frac{[I]}{IC_{50}}\right)^{\text{slope}}}
\]

where \([I]\) is inhibitor concentration, \(Y_{\min}\) is minimum percentage activity in relation to control, \(Y_{\max}\) is percentage activity when there is no inhibitor present, and slope is the slope of the curve. Four-parameter fitting was used for the IC50 estimation for all fittings.

Combined DDI index for each transporter was calculated by adding unbound \(C_{\max}\) (\(I_u\)) divided by IC50 of abemaciclib, M2, and M20, as described by Lutz and Isoherranen36:

\[
\text{Combined DDI index} = \frac{I_{u,\text{Abemaciclib}}}{IC50\text{ abemaciclib}} + \frac{I_{u,M2}}{IC50 M2} + \frac{I_{u,M20}}{IC50 M20}
\]

Figure 4 Mean serum creatinine (a), cystatin-C (b), and neutrophil gelatinase-associated lipocalin (NGAL) (c) concentrations following a single oral dose of placebo or 400 mg abemaciclib with a single oral dose of 1,000 mg metformin or a single infusion of 3.235 g iohexol in healthy subjects up to 24 hours postdose. Data is presented ± SD.
Figure 5 Creatinine-corrected urine kidney injury molecule (KIM)-1 and neutrophil gelatinase-associated lipocalin (NGAL) concentrations following a single oral dose of placebo or 400 mg abemaciclib with a single oral dose of 1,000 mg metformin or a single infusion of 3.235 g iohexol in healthy subjects up to 96 hours postdose. The middle line in each box plot represents the median, the top and bottom margins of the box represent the 75th and 25th percentiles. The whiskers extend to the 90th and 10th percentiles. Data extending beyond the 90th and 10th percentiles are plotted individually.
Bioanalytical methods
Abemaciclib and metformin concentrations were measured in plasma and/or urine (as applicable), at Q2 Solutions (Ithaca, NY) and Covance Laboratories (Madison, WI), and iohexol concentrations were measured in plasma at Covance Bioanalytical Services (Indianapolis, IN) using validated liquid chromatograph tandem mass spectrometric methods.
Renal biomarkers were measured in serum and/or urine (as applicable) at Covance Central Laboratory Services (Indianapolis, IN).

Clinical study design
A randomized, single-center, single-blind, four-period, placebo-controlled crossover study was conducted in healthy subjects (n = 40) at Covance Clinical Research Unit, Dallas, TX. An independent ethical review board (Midlands Institutional Review Board, Kansas) reviewed and approved the trial protocol. The trial was registered at ClinicalTrials.gov (NCT02884089). Enrolled subjects received each of four dosing regimens (400 mg oral abemaciclib or placebo followed 5 hours later by 1,000 mg oral metformin and 400 mg abemaciclib or placebo followed 8 hours later by 3,235 mg iohexol administered as a 15-minute i.v. infusion) according to a randomized schedule. A 400-mg dose of abemaciclib was administered, as this was expected to achieve plasma concentrations approximating steady state following twice-daily dosing with 200 mg, and doses were timed such that the peak plasma concentrations of the coadministered drugs coincided. Subjects underwent a meal stabilization period of 3 days prior to dosing in order to minimize variation in SCr from diet.
Following study drug administration, timed blood samples were collected up to 120 hours post abemaciclib dose, 36 hours post metformin dose and 6 hours post iohexol dose for assessment of the respective analyte concentrations in plasma. Urine metformin concentrations were also assessed. Blood and urine were also collected up to 120 hours postdose for analysis of renal biomarkers serum cystatin-C, NGAL, and creatinine, creatinine CL, and urinary concentrations of NGAL, KIM-1, and creatinine, respectively. Study periods were separated by at least 16 days, except the placebo/metformin dosing period after which there was at least 5 days of separation.

Statistical analysis
PK parameter estimates for metformin and abemaciclib were calculated using standard noncompartmental methods using Phoenix WinNonlin software version 6.4 (Certara USA, Princeton, NJ). Iohexol PK parameters were calculated using a two-compartment i.v. infusion model. Metformin CL in urine collected for 36 hours by the AUROC0-36. In general, CL in urine collected for 36 hours by the AUROC0-36 is given by:

\[ CL_{urine} = (\text{GFR} \times fu,p + CL_{R}) - F \times (\text{GFR} \times fu,p + CL_{R}) \]  

where fu,p is the fraction unbound in plasma for metformin, which was assumed to be unity (reference), and is the clearance of renal secretion, and F is the fraction of metformin entering the renal tubule that is reabsorbed. In this analysis, we assumed that renal tubular reabsorption was negligible and F was set to zero. Metformin CL in urine collected for 36 hours by the AUROC0-36 was calculated for each subject as follows (Eq. 4):

\[ CL_{R, urine} = CL_{R, placebo} - GFR_{placebo} \]  

\[ CL_{R, urine} \text{ (test)} = CL_{R, abemaciclib} - GFR_{abemaciclib} \]  

PK parameter estimates for plasma and urine were evaluated to delineate effects of abemaciclib on metformin PK. Log-transformed Cmax*, AUC0-36*, CL in plasma and urine (as applicable), at Q2 Solutions (Ithaca, NY) and Covance Laboratories (Madison, WI), and iohexol concentrations were measured in plasma at Covance Bioanalytical Services (Indianapolis, IN) using validated liquid chromatograph tandem mass spectrometric methods.
Renal biomarkers were measured in serum and/or urine (as applicable) at Covance Central Laboratory Services (Indianapolis, IN).
The GFR was analyzed using a similar method to that described for metformin PK, in which iohexol with abemaciclib was the test and iohexol with placebo was the reference. The eGFR was calculated using SCr or cystatin-C using the CKD-EPI creatinine or cystatin-C equations.
Statistical analyses were performed using SAS version 9.3 (SAS Institute, Cary, NC).
Analysis of exploratory biomarkers
End points for biomarker and safety analyses included serum concentrations of cystatin-C, NGAL, and creatinine, creatinine CL, and urinary concentrations of NGAL, KIM-1, and creatinine. Renal biomarker concentrations at the time of maximal creatinine concentration were calculated for each dosing period. Ratios of urine renal biomarkers to urine creatinine were calculated.

SUPPORTING INFORMATION
Supplementary information accompanies this paper on the Clinical Pharmacology & Therapeutics website (www.cpt-journal.com).
Figure S1. Clinical study subject disposition.
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J.C.C., P.K.T., Y.A.P., J.B., A.Y.C., S.D.H., and P.K. are current or former employees of Eli Lilly.
AUTHOR CONTRIBUTIONS
J.C.C., P.K.T., Y.A.P., J.B., A.Y.C., J.R., S.D.H., P.K., and J.V.B. analyzed the data.

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