Evaluation of Potential Drug-Drug Interaction Risk of Pexidartinib With Substrates of Cytochrome P450 and P-Glycoprotein

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Abstract

Pexidartinib is approved for treatment of adults with symptomatic tenosynovial giant cell tumor. In vitro data showed pexidartinib’s potential to inhibit and induce cytochrome P450 (CYP) 3A, inhibit CYP2C9, CYP2C19 and P-glycoprotein (P-gp). Herein, 2 open-label, single-sequence, crossover studies evaluated the drug-drug interaction potential of pexidartinib on CYP enzymes (CYP2C9, CYP2C19, and CYP3A) and P-gp. Thirty-two subjects received single oral doses of midazolam (CYP3A substrate) and tolbutamide (CYP2C9 substrate) alone and after single and multiple oral doses of pexidartinib. Twenty subjects received single oral doses of omeprazole (CYP2C19 substrate) and digoxin (P-gp substrate) alone or with pexidartinib. Analysis of variance was conducted to determine the effect of pexidartinib on various substrates’ pharmacokinetics. No drug-drug interaction was concluded if the 90% confidence interval of the ratio of test to reference was within the range 80% to 125%. Coadministration of single and multiple doses of pexidartinib resulted in 21% and 52% decreases, respectively, in the area under the plasma concentration–time curve from time zero to the last measurable time point (AUClast) of midazolam, whereas AUClast values of tolbutamide increased 15% and 36%, respectively. Omeprazole exposure decreased on concurrent administration with pexidartinib, the metabolite-to-parent ratio was similar following omeprazole administration alone vs coadministration with pexidartinib; pexidartinib did not affect CYP2C19-mediated metabolism. Maximum plasma concentrations of digoxin slightly increased (32%) with pexidartinib coadministration; no significant effect on digoxin AUClast. These results indicate that pexidartinib is a moderate inducer of CYP3A and a weak inhibitor of CYP2C9 and does not significantly affect CYP2C19-mediated metabolism or P-gp transport.

Keywords
cytochrome P450, drug interaction, P-glycoprotein, pexidartinib, pharmacokinetics

Pexidartinib is a novel oral small-molecule inhibitor that selectively targets colony-stimulating factor 1 receptor, KIT proto-oncogene receptor tyrosine kinase (KIT), and FMS-like tyrosine kinase 3 harboring an internal tandem duplication mutation.¹ ² After oral administration, maximum pexidartinib plasma concentrations (Cmax) are achieved in ≈2.5 hours (tmax).³ Administration of pexidartinib with a high-fat meal doubles pexidartinib exposure and delays tmax by 1.5 hours. Metabolism of pexidartinib is primarily mediated via oxidation by cytochrome P450 (CYP) 3A and glucuronidation by uridine glucuronyl transferase (UGT) 1A4.⁴ The elimination half-life of pexidartinib is 26.6 hours. On multiple dosing as a twice-daily regimen, pexidartinib exposure becomes ≈3.6 times the exposure after the first dose (the accumulation ratio).³

The CYP family of enzymes plays an important role in the oxidative metabolism of many drugs.³ ⁴ Unpublished in vitro studies suggest that pexidartinib has the potential to inhibit multiple CYP enzymes (predicted steady-state Cmax of pexidartinib > half maximal inhibitory concentration [IC50]) and transporters (gut concentration of pexidartinib >IC50), including CYP3A, CYP2C9, CYP2C19, and P-glycoprotein (P-gp). Additionally, in vitro data

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indicate that pexidartinib has the potential to induce CYP3A. Furthermore, pexidartinib is expected to be administered chronically over a long period of time, and it is likely that many patients receiving pexidartinib will be receiving concomitant medications at some point during their treatment course. Therefore, it is important to evaluate the effect of pexidartinib on substrates of these CYP enzymes and P-gp to determine whether pexidartinib is associated with clinically meaningful drug-drug interactions (DDIs) in vivo.

This report describes the results of 2 open-label, single sequence, crossover studies designed to evaluate the perpetrator drug interaction potential of pexidartinib. The primary objective of these studies was to evaluate the effect of pexidartinib on CYP3A, CYP2C9, CYP2C19, and P-gp using midazolam, tolbutamide, omeprazole, and digoxin as probe drugs, respectively.

Materials and Methods

The protocol for each study was approved by local or central Institutional Review Boards (IRBs). For the midazolam/tolbutamide study, the central IRB was Western IRB, Puyallup, Washington, while local IRBs were at the University of Kansas, Kansas City, Kansas; Mary Crowley Medical Research Center, Dallas, Texas; Dana-Farber Cancer Institute, Boston, Massachusetts; Stanford University Research Compliance Office, Palo Alto, California; the Leiden University Medical Center, Leiden, The Netherlands; The National Taiwan University Hospital, Taipei City, Taiwan; and the Northern A Health and Disability Ethics Committee Ministry of Health, Wellington, New Zealand. For the omeprazole/digoxin study, a central IRB (IntegReview IRB, Austin, Texas) was used. All subjects provided written informed consent before participation in the study. The studies were conducted in compliance with the ethical principles of the Declaration of Helsinki and in accordance with International Council for Harmonisation E6 Guideline for Good Clinical Practices and applicable regulatory requirements. The midazolam/tolbutamide study was conducted at 11 sites in the United States, Taiwan, the Netherlands, and New Zealand and the omeprazole/digoxin study was conducted at Worldwide Clinical Trials Early Phase Services, San Antonio, Texas.

The 2 studies assessed the drug interaction potential of pexidartinib as a perpetrator according to US Food and Drug Administration (FDA) and European Medicines Agency guidance on DDIs. One study evaluated how single and multiple oral doses of pexidartinib affect the pharmacokinetics (PK) of midazolam (a probe substrate of CYP3A) and tolbutamide (a probe substrate of CYP2C9). The second study evaluated the effect of a single oral dose of pexidartinib on the PK of omeprazole (a probe substrate of CYP2C19) and digoxin (a probe substrate of P-gp).

Study Designs

Midazolam/Tolbutamide (CYP3A/CYP2C9 Substrate) Drug-Drug Interaction Study (Study U126). This was a 2-part, phase 1, open-label, single sequence study in individuals with tenosynovial giant cell tumor (TGCT) or a malignancy for which there was a biologic rationale for administration of colony-stimulating factor 1 receptor or KIT inhibitors. The primary objective of part 1, which spanned 15 days, was to assess the DDI potential of pexidartinib. Study medication was administered in the following sequence during part 1:

- Day 1: Subjects received a single oral dose of midazolam 2 mg and tolbutamide 500 mg in the fasted state.
- Day 3: Subjects began receiving oral pexidartinib 400 mg twice daily in a fasted state.
- Days 3 and 13: Single oral doses of midazolam 2 mg and tolbutamide 500 mg were coadministered with the morning doses of pexidartinib in a fasted state.

Following completion of part 1, subjects continued with pexidartinib treatment in part 2 until there was no longer clinical benefit or until other reasons for discontinuation were met.

Omeprazole/Digoxin (CYP2C19, P-gp Substrate) DDI Study (Study U127). This was a phase 1, open-label, 4-treatment, 4-period, single-sequence study in healthy subjects. In contrast to the midazolam/tolbutamide study, a single-dose study was considered adequate for the evaluation of CYP2C19 and P-gp (omeprazole/digoxin) since in vitro data suggest that potential inhibitory effect of pexidartinib on CYP2C19 and P-gp is not time dependent. Pexidartinib was administered as a single oral dose of 1800 mg (9 capsules of 200 mg each) in an effort to attain the maximum concentration at steady state. Eligible subjects were confined to the investigational clinical site for approximately 18 days starting on day −1. Subjects received the 4 treatments in a fixed sequence in the fasted state:

- Day 1: oral omeprazole 40 mg
- Day 2: oral digoxin 0.25 mg
- Day 6: oral pexidartinib 1800 mg plus omeprazole 40 mg
- Day 14: oral pexidartinib 1800 mg plus digoxin 0.25 mg

Study Population

Midazolam/Tolbutamide (CYP3A, CYP2C9 Substrate) Study (Study U126). Subjects with histopathologically
diagnosed tumor (TGCT, KIT-mutant tumor, or other solid tumor) who were ≥18 years of age, not pregnant, using highly effective contraception, and with adequate hematology (absolute neutrophil count ≥1.5 × 10⁹/L; hemoglobin >10 g/dL; platelet count ≥100 × 10⁹/L), hepatic, (liver transaminases and total bilirubin at or below the upper limit of normal) and renal function (serum creatinine ≤1.5 × upper limit of normal) were eligible for inclusion. Subjects with HIV or hepatitis C virus infection or who had positive hepatitis B surface antigen, hepatobiliary diseases (eg, biliary tract diseases, autoimmune hepatitis, inflammation, fibrosis, cirrhosis) were excluded from enrollment. Other exclusion criteria included poor metabolizer status of CYP2C9 (via genotyping at screening) and those on potent CYP2C9, CYP3A, or UGT family 1 member A4 inhibitors and inducers or potent P-gp inhibitors and inducers unless discontinued at least 14 days before study drug administration. Antitumor or investigational agents were not allowed within 4 weeks of the study. Herbal medications were not allowed.

Omeprazole/Digoxin (CYP2C19, P-gp Substrate) Study (Study U127). This study included healthy, nonsmoking men and nonpregnant women aged 18 to 60 years with a body mass index (BMI) of 18 to 32 kg/m². Subjects were excluded if electrocardiogram abnormalities or renal, hepatic, cardiac, cardiovascular, psychological, pulmonary, metabolic, neurologic, or other medical disorders were found. CYP2C19 poor metabolizers (via genotyping at screening) and those using a moderate or strong inhibitor or inducer of CYP3A, CYP2C9, CYP1C19, or UGT within 2 weeks before dosing and throughout the study were also excluded. Use of any prescription or over-the-counter medication (including herbals) was not allowed within 14 days of the study.

Study Assessments
In the midazolam/tolbutamide (CYP3A, CYP2C9 substrate) study, plasma samples for analysis of midazolam, 1-hydroxy midazolam, tolbutamide, and 4-hydroxy tolbutamide were collected at predose and at 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 24, and 48 hours on days 1 to 3 and also when coadministered with pexitardinib on days 3 to 5 and days 13 to 15. In the meprazole/digoxin (CYP2C19, P-gp substrate) study, plasma samples for analysis of meprazole, 5-hydroxy meprazole, and digoxin were collected before dosing and at 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10, 12, and 24 hours postdose after administration of meprazole or digoxin, after administration of each drug alone or in combination with pexitardinib. Samples were also taken at 36, 48, 72, and 96 hours postdose for analysis of digoxin. Assay details for determination of agents coadministered with pexitardinib are summarized in the Supplemental Information.

Safety. Safety assessments for both studies included adverse events (AEs), laboratory tests, vital signs, physical examination, and electrocardiograms. AEs were assessed for severity and relationship to study medication. Grading of AEs was performed according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.

Data Analysis
In both studies, determination of sample sizes was primarily based on the ability to provide a predefined magnitude of precision for DDIs. In the midazolam/tolbutamide study, a sample size of 24 was required to provide a ≥80% power to conclude the absence of effect of pexitardinib on the area under the plasma concentration–time curve from time zero to infinity (AUCinf) of tolbutamide when the true ratio is <1.05. In the meprazole/digoxin study, a sample size of 16 was required to provide a >80% power to conclude the absence of an effect of pexitardinib on AUC from time zero to the last measurable time point (AUClast) when the true ratio is <1.05. The safety analysis sets for both studies included all subjects who received at least 1 dose of pexitardinib. The PK analysis sets included all subjects who received at least 1 dose of study drugs and had a measurable plasma concentration.

Plasma concentration–time data were analyzed using noncompartmental methods using WinNonlin (Certara USA Inc, Princeton, New Jersey). Derived PK parameters included $C_{\text{max}}$, $t_{\text{max}}$, AUClast, and AUCinf. The metabolite-to-parent ratio (MPR) for the substrate drugs (midazolam, tolbutamide, and meprazole) was derived to help understand the impact on the metabolic pathway. Descriptive statistics of PK parameters by analyte and treatment (reference and test) were generated. When the victim drug was administered alone, PK parameters were considered “reference” and when administered with pexitardinib were considered “test.” An analysis of variance model with treatment and subjects as fixed effects was used to compare natural-log-transformed PK parameters ($C_{\text{max}}$, AUClast, AUCinf) of substrates with and without the coadministration of pexitardinib. Geometric mean ratios and their corresponding 90% confidence intervals (CIs) were calculated by anti-log transformation. No DDI was concluded if the 90%CI of the ratio of the test to the reference was completely within the range of 0.80 and 1.25 for $C_{\text{max}}$, AUClast, and AUCinf.
Figure 1. Mean plasma midazolam (A) and tolbutamide (B) concentrations after a single dose of pexidartinib and after 10 days of coadministered pexidartinib on semi-logarithmic scales.

Results

Study Population

Midazolam/Tolbutamide (CYP3A, CYP2C9 Substrate) Study (Study U126). Thirty-two subjects were enrolled, and all were included in the PK analysis set for summary statistics. For statistical comparison (analysis of variance), 2 subjects were excluded since they discontinued the study before initiation of pexidartinib treatment. The 30 subjects in the full/safety analysis set (ie, those who received pexidartinib) had a mean age of 50.8 (SD, 19.3) years and a mean BMI of 26.1 (SD, 7.9) kg/m². Among the subjects, there was an equal distribution of men and women (50% each) and the population was predominantly White (77%) and then Asian (17%). Tumor types included TGCT (n = 9), KIT-mutant gastrointestinal stromal tumor (n = 4), and other (n = 17).

Omeprazole/Digoxin (CYP2C19, P-gp Substrate) Study (Study U127). Of the 20 subjects enrolled, 19 competed the study and were included in the PK analysis. Sixteen (80%) were men, 10 (50%) were White, and 8 (40%) were Black. The mean age was 40.3 (SD, 11.4) years, and the mean BMI was 27.7 (SD, 2.6) kg/m².
Pharmacokinetics

**Midazolam/Tolbutamide (CYP3A, CYP2C9 Substrate) Study (Study U126).** Maximum midazolam concentrations after a single dose were seen at \( \approx 0.5 \) hours when administered alone or after coadministration of either single or multiple oral doses of pexidartinib (Figure 1A). After a single dose, coadministration of midazolam and pexidartinib resulted in a 9% lower midazolam \( C_{\text{max}} \) value and a 21% decrease in \( AUC_{\text{last}} \). After multiple doses of pexidartinib, single-dose \( C_{\text{max}} \) of midazolam was decreased by 28% and \( AUC_{\text{last}} \) was decreased by 52%. The 90%CI values were outside the 80% to 125% no-effect boundaries for both \( C_{\text{max}} \) and \( AUC_{\text{last}} \) after multiple doses of pexidartinib (Table 1). Exposure to 1-hydroxy midazolam was similar with or without concomitant administration of pexidartinib. However, the MPR of midazolam doubled after multiple-dose pexidartinib administration, increasing from 5.87 when midazolam was administered alone to 12.2 following multiple doses of pexidartinib.

Mean plasma concentrations of single-dose tolbutamide after coadministration of single and multiple oral doses of pexidartinib are illustrated in Figure 1B. Maximum tolbutamide concentrations were observed at \( \approx 3 \) hours postdose when administered alone or with single or multiple doses of pexidartinib. Coadministration of tolbutamide and pexidartinib resulted in no significant change in tolbutamide \( C_{\text{max}} \) or \( AUC_{\text{last}} \) after a single dose of pexidartinib (Table 1). After multiple doses of pexidartinib, coadministration of tolbutamide resulted in no significant effect on \( C_{\text{max}} \), but there was a significant effect on \( AUC_{\text{last}} \) (36% increase), with 90%CI values falling outside the 80% to 125% no-effect boundary (Table 1). There was a decrease in exposure to 4-hydroxy tolbutamide during pexidartinib coadministration, with MPR decreasing from 2.35% when tolbutamide was administered alone to 1.38% when coadministered with multiple doses of pexidartinib.

**Omeprazole/Digoxin (CYP2C19, P-gp Substrate) Study (Study U127).** Mean plasma concentrations of single doses of omeprazole and digoxin when administered alone and following a single oral dose of pexidartinib are summarized in Figure 2. The statistical analysis

### Table 1. Statistical Comparison of Midazolam (A) and Tolbutamide (B) Pharmacokinetic Exposure Parameters When Administered Alone or With Pexidartinib

|                      | N     | Midazolam Alone | Midazolam After First Dose of Pexidartinib | Geometric LS Mean Ratio (%) | 90%CI          |
|----------------------|-------|-----------------|-------------------------------------------|----------------------------|---------------|
|                      |       |                 |                                           |                            |               |
| \( C_{\text{max}} \) (ng/mL) | 30    | 12.2            | 11.2                                      | 91.5                       | 82.0-102.0    |
| \( AUC_{\text{last}} \) (ng·h/mL) | 30    | 35.7            | 28.3                                      | 79.4                       | 72.3-87.1*    |
| \( AUC_{\text{inf}} \) (ng·h/mL) | 30    | 38.8            | 32.0                                      | 82.6                       | 73.9-92.3*    |

|                      | N     | Tolbutamide Alone | Tolbutamide After Single-Dose Pexidartinib | Geometric LS Mean Ratio (%) | 90%CI          |
|----------------------|-------|-------------------|-------------------------------------------|----------------------------|---------------|
|                      |       |                   |                                           |                            |               |
| \( C_{\text{max}} \) (ng/mL) | 30    | 42 705.4          | 42 973.5                                  | 100.6                      | 94.3-107.4    |
| \( AUC_{\text{last}} \) (ng·h/mL) | 30    | 470 031.4         | 538 730.5                                 | 114.6                      | 105.9-124.1   |
| \( AUC_{\text{inf}} \) (ng·h/mL) | 30    | 510 710.3         | 546 942.5                                 | 107.1                      | 101.1-113.5   |

|                      | N     | Tolbutamide Alone | Tolbutamide After Multiple-Dose Pexidartinib | Geometric LS Mean Ratio (%) | 90%CI          |
|----------------------|-------|-------------------|----------------------------------------------|----------------------------|---------------|
|                      |       |                   |                                              |                            |               |
| \( C_{\text{max}} \) (ng/mL) | 30    | 42 705.4          | 40 515.7                                   | 94.9                       | 88.5-101.7    |
| \( AUC_{\text{last}} \) (ng·h/mL) | 30    | 470 031.4         | 638 005.4                                  | 135.7                      | 123.8-148.8*  |
| \( AUC_{\text{inf}} \) (ng·h/mL) | 30    | 5 13 259.7        | 660 520.8                                  | 128.7                      | 118.3-139.9*  |

AUC<sub>inf</sub>, area under the plasma concentration–time curve from time zero to infinity; AUC<sub>last</sub>, area under the plasma concentration–time curve from time zero to the last measurable concentration; CI, confidence interval; C<sub>max</sub>, maximum observed concentration; LS, least squares.

<sup>a</sup>Geometric least squares mean.

<sup>b</sup>Values outside the 80% to 125% no-effect boundary.
Figure 2. Mean plasma omeprazole (A) and digoxin (B) concentrations when administered alone or with a single dose of pexidartinib on semi-logarithmic scales.

Comparing omeprazole and digoxin pharmacokinetics with and without pexidartinib is summarized in Table 2. Coadministration of single doses of pexidartinib and omeprazole resulted in a delayed omeprazole $t_{\text{max}}$ (from 2.25 to 3 hours), a 37% decrease in $C_{\text{max}}$ for omeprazole, and a 23% to 24% decrease in $AUC_{\text{last}}$ for omeprazole and 5-hydroxy omeprazole. The 90%CI values for both $C_{\text{max}}$ and $AUC_{\text{last}}$ of omeprazole fell outside the 80% to 125% no-effect boundary (Table 2). The mean MPR was similar for omeprazole when administered alone (0.730 [SD, 0.488]) or in combination with pexidartinib (0.722 [SD, 0.431]).

Coadministration of pexidartinib and digoxin resulted in a 32% increase in $C_{\text{max}}$, but there was no apparent effect on the time to reach $C_{\text{max}}$ or the shape of the plasma concentration–time curve (Figure 2B). Pexidartinib coadministration also was associated with a nonsignificant effect on the $AUC_{\text{last}}$ of digoxin, with an increase of 8%.

**Safety**

In the midazolam/tolbutamide study involving 30 subjects with tumors, the majority of treatment-emergent adverse events (TEAEs) were grade 1 or 2. The most common AEs were fatigue (37%), hair color changes (33%), and anemia (27%). Twelve subjects (40%) experienced 22 grade 3 TEAEs, of which 9 (anemia, esophagitis, hypersensitivity, drug hypersensitivity, increased alanine aminotransferase, increased aspartate aminotransferase, increased gamma-glutamyltransferase, increased blood cholesterol, increased blood alkaline phosphatase) were considered related to pexidartinib, and 4 subjects experienced a grade 4 TEAE, of
Table 2. Statistical Analysis of Exposure of Omeprazole and Digoxin With and Without Coadministration of Pexidartinib (N = 19)

|                      | Omeprazole Only a | Omeprazole Plus Pexidartinib b | Geometric LS Mean Ratio (%) | 90%CI          |
|----------------------|-------------------|--------------------------------|-----------------------------|----------------|
| Omeprazole + single-dose pexidartinib |                   |                                |                             |                |
| C_{max} (ng/mL)      | 907.8             | 570.2                          | 62.8                        | 53.1-74.3      |
| AUC_{last} (ng · h/mL)| 1727.1           | 1336.3                         | 77.4                        | 67.4-88.8      |
| AUC_{inf} (ng · h/mL)| 1740.4           | 1447.3                         | 83.2                        | 73.1-94.6      |
| Digoxin Only a       |                   |                                |                             |                |
|                      |                   |                                |                             |                |
| Digoxin + single-dose pexidartinib |                   |                                |                             |                |
| C_{max} (ng/mL)      | 1.2               | 1.5                            | 131.6                       | 118.1-146.7    |
| AUC_{last} (ng · h/mL)| 16.3             | 17.6                           | 108.2                       | 100.6-116.4    |
| AUC_{inf} (ng · h/mL)| 18.6             | 20.4                           | 109.3                       | 98.9-120.7     |

AUC_{inf} area under the plasma concentration–time curve from time zero to infinity; AUC_{last}, area under the plasma concentration–time curve from time zero to the last measurable concentration; CI, confidence interval; C_{max}, maximum observed concentration; LS, least squares.

aGeometric least squares mean.

which 1 (increased bilirubin) was considered related to pexidartinib.

Two subjects (7%) in the midazolam/tolbutamide study discontinued treatment due to pexidartinib-related TEAEs (drug hypersensitivity, increased blood bilirubin). In the omeprazole/digoxin study in 20 healthy subjects, 8 (40%) experienced a TEAE, all of which were mild (grade 1) in intensity. Three of these events (all pruritus) were considered related to pexidartinib.

Discussion

These studies were initiated to determine the in vivo potential effect of oral pexidartinib on substrates of these CYP isozymes and transporters according to FDA and European Medicines Agency DDI guidances.6,7 The midazolam/tolbutamide (CYP3A and CYP2C9 substrates) study was a multiple-dose study because in vitro data suggested that pexidartinib can be both a direct and time-dependent inhibitor and an inducer of CYP3A and an inhibitor of CYP2C9. In the omeprazole/digoxin study in 20 healthy subjects, 8 (40%) experienced a TEAE, all of which were mild (grade 1) in intensity. Three of these events (all pruritus) were considered related to pexidartinib.

Overall, the results indicate that pexidartinib is a moderate inducer of CYP3A and a weak inhibitor of CYP2C9 (based on FDA criteria6), suggesting that pexidartinib may decrease exposure to coadministered drugs that are substrates of CYP3A and increase exposure to coadministered drugs that are substrates of CYP2C9. Coadministration of a single dose of pexidartinib with the CYP3A substrate midazolam resulted in a 21% decrease in midazolam AUC_{last}. After multiple doses of pexidartinib, the decrease in midazolam AUC_{last} was even greater (52%). The decreased exposure of midazolam after multiple doses of pexidartinib indicates that in vivo the CYP3A induction effect of pexidartinib is more pronounced than its CYP3A inhibitory effect. However, the observed decreased exposure of midazolam when coadministered with the first dose of pexidartinib is not consistent with direct inhibition of CYP3A by pexidartinib. This observation could be explained by the possible CYP3A activation effect of pexidartinib. In fact, in vitro, pexidartinib activated midazolam hydroxylation in human liver microsome in a concentration-dependent manner (unpublished data). Overall, the decreased exposure of midazolam on concurrent administration with pexidartinib also suggests that the metabolism of drugs that are metabolized via CYP3A (eg, estradiol) may be enhanced with concomitant pexidartinib administration, leading to a potential for decreased therapeutic effect of the victim drugs. This interaction will be most clinically relevant for drugs with a narrow therapeutic index (eg, sirolimus, tacrolimus, cyclosporine), where modest decreases in substrate concentrations result in clinically meaningful differences in the risk:benefit ratio.8,9

Single oral doses of pexidartinib had no significant effect on the exposure of the CYP2C9 substrate tolbutamide, but there was a 36% increased exposure (AUC_{last}) of tolbutamide after multiple doses of...
Pexidartinib, indicating that pexidartinib is a weak inhibitor of CYP2C9. This small increase in exposure of CYP2C9 substrates with concomitant pexidartinib administration is unlikely to be clinically meaningful except for coadministered CYP2C9 substrates that have a narrow therapeutic index (eg, warfarin). However, since coagulation parameters are already routinely assessed during warfarin administration, this interaction can generally be managed by appropriate warfarin dose adjustments.

In the CYP2C19 study, coadministration of single oral doses of pexidartinib and omeprazole resulted in a 37% decrease in omeprazole Cmax and a 17% to 23% decrease in omeprazole AUCs and a similar decrease in 5-hydroxy omeprazole exposure. This result was not expected since pexidartinib is an inhibitor of CYP2C19 in vitro with an IC50 value of 9.3 μmol/L. Additionally, generation of 5-hydroxy omeprazole (as determined by the MPR and an indicator of CYP2C19-mediated metabolism of omeprazole) was not influenced by the coadministration of omeprazole with pexidartinib. Since 5-hydroxy omeprazole is generated via the CYP2C19 pathway, the lack of an effect on the MPR suggests that the effect of pexidatinib on the PK of omeprazole is related to mechanisms other than CYP2C19-mediated metabolism of omeprazole. The decreased exposure of omeprazole when coadministered with pexidartinib could possibly be due to decreased absorption/bioavailability of omeprazole when coadministered with pexidartinib. It is possible that omeprazole got trapped in the matrix created by the large number of pexidartinib capsules. In the clinical setting, the highest recommended dose of pexidartinib is 400 mg (2 capsules of 200 mg each) administered twice daily.1 Therefore, a situation like this will not arise in the clinical setting.

In the U127 study, coadministration of pexidartinib resulted in a 32% increase in digoxin Cmax and a small increase in AUClast (8%). The increase in Cmax of digoxin when coadministered with pexidartinib is consistent with the gut P-gp inhibition by pexidartinib.

Preclinical data indicate that the in vitro IC50 of pexidartinib for P-gp is 43.4 μmol/L (data on file). At a dose of 400 mg twice daily, pexidartinib gut concentrations will be ≈88.2 times (gut concentration/IC50) the in vitro IC50, whereas the predicted steady-state Cmax of pexidartinib in TGCT patients will be half of IC50. Therefore, pexidartinib has the potential to inhibit gut P-gp but not renal P-gp. However, the extent of the effect of pexidartinib on the gut P-gp may not have been fully characterized in this study. This is because digoxin is somewhat insensitive for assessing intestinal P-gp inhibition due to its moderate to high bioavailability (relative bioavailability: 60%-80%).2,10 Pexidartinib was generally well tolerated in both studies with safety results generally consistent with the previously defined safety profile of pexidartinib.1,11 As expected, rates of AEs were higher for subjects with tumors (midazolam/tolbutamide studies) than for healthy subjects (omeprazole/digoxin studies). Overall, the types and severity of AEs in subjects with tumors were generally similar to those reported in the phase 3 trial in patients with TGCT.1,11

Limitations of the study include the potential effects of genetic polymorphisms on the DDI risk. While poor metabolizers of CYP2C9 and CYP2C19 were excluded, intersubject variability in CYP2C9 and CYP2C19 metabolism has been documented even among extensive metabolizers.12,13 Further, there are ethnic differences in CYP polymorphisms between ethnic groups with differences in rates of poor and extensive metabolizers of common CYP enzymes systems, which may impact the overall extent of DDI across populations.14

Conclusions
These results indicate that pexidartinib is a moderate inducer of CYP3A and a weak inhibitor of CYP2C9. However, the data do not support an effect of pexidatinib on CYP2C19-mediated metabolism or a clinically relevant DDI potential for P-gp substrate. Physicians and pharmacists should be aware of the potential impact on the PK of concomitant medications metabolized by these isozymes when pexidartinib is prescribed.

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Conflicts of Interest
H.Z., F.K., Q.W., and J.G. are employees of Daiichi Sankyo, the study sponsor. C.Z. is an employee of Worldwide Clinical Trials, where the study was performed. M.S.G. reports institutional research support from MedImmune, Merck, BMS, Amgen, Tesaro, Beigene, AbbVie, Aeglea, Agenus, Arcus, Astex, Blueprint, Calithera, Celldex, Corcept, Clovis, Eli Lilly, Endocyte, Five Prime, Genocea, Neon, Plexikon, Imaging Endpoints, Revolution Medicine, Seattle Genetics, Serono, SynDevRx, Tolero, Tracon, Deciphera, and Salarius. H.M.B. served as a consultant for Celgene, Endocyte, Bayer, and Guradant360; reports honoraria from Bayer and SirTx; and participated in an advisory board for Tracon. A.J.W. reports grants to his institution from Daiichi Sankyo, Eli Lilly, Five Prime Therapeutics, Plexikon, Karyopharm Therapeutics, AADi Inc, and Celldex; and served as a consultant for Daiichi Sankyo, Eli Lilly, Five Prime Therapeutics, Loxo, and Novartis. R.G. declares no conflicts of interest.
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Data Sharing
Deidentified individual participant data and applicable supporting clinical study documents may be available upon request at https://www.clinicalstudydatarequest.com/. In cases where clinical study data and supporting documents are provided pursuant to the sponsor’s policies and procedures, the sponsor will continue to protect the privacy of the clinical study participants. Details on data-sharing criteria and the procedure for requesting access can be found at this web address: https://www.clinicalstudydatarequest.com/Study-Sponsors/Study-Sponsors-DS.aspx.

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