

Effect of Mild and Moderate Hepatic Impairment (Defined by Child–Pugh Classification and National Cancer Institute Organ Dysfunction Working Group Criteria) on Pexidartinib Pharmacokinetics

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Abstract

Pexidartinib is a novel oral small-molecule tyrosine kinase inhibitor targeting the colony-stimulating factor 1 receptor. Pexidartinib undergoes extensive hepatic metabolism via multiple cytochrome P450 and uridine 5'-diphospho-glucuronosyl transferase enzymes, with ZAAD-1006a as the only major metabolite in human plasma. As pexidartinib is extensively metabolized, hepatic impairment (HI) could lead to increased exposure to pexidartinib. The objective of the two phase I, open-label studies was to determine the pharmacokinetics of pexidartinib after a single 200-mg dose in subjects with mild and moderate HI, based on Child–Pugh classification (PL3397-A-UI23: 8 mild HI and 8 moderate HI vs 16 matched healthy controls) and National Cancer Institute Organ Dysfunction Working Group (NCI-ODWG) criteria (PL3397-A-UI29: 8 moderate HI versus 8 matched healthy controls [NCT04223635]). Based on Child–Pugh classification, exposure to pexidartinib (maximum observed concentration [C_{max}], area under the plasma concentration–time curve up to the last measurable concentration [AUC_{last}], and extrapolated to infinity [AUC_{inf}]) was similar in subjects with mild and moderate HI and in respective matched healthy controls, whereas ZAAD-1006a exposure (AUC) was approximately 27% to 28% and 41% to 48% higher in mild and moderate HI, respectively. According to NCI-ODWG criteria, total pexidartinib exposure was 42% to 46% higher in subjects with moderate HI, compared with healthy controls, and total ZAAD-1006a exposure was 70% to 79% higher for subjects with moderate HI, compared with matched healthy controls with normal hepatic function. These findings were used to develop appropriate dose recommendations in patients with hepatic impairment.

Keywords

Child–Pugh, hepatic impairment (HI), mild HI, moderate HI, NCI-ODWG, pexidartinib, pharmacokinetics, tenosynovial giant cell tumor (TGCT), ZAAD-1006A

Pexidartinib is a novel oral small-molecule inhibitor that selectively targets colony-stimulating factor 1 receptor (CSF1R),^{1–4} KIT proto-oncogene receptor tyrosine kinase (KIT), and FMS-like tyrosine kinase 3 (FLT3), harboring an internal tandem duplication mutation.^{5,6} Pexidartinib is approved in the USA at a dosage of 400 mg orally, twice daily, and was added by the National Comprehensive Cancer Network (NCCN) as a category-1 recommendation for the treatment of adult patients with symptomatic tenosynovial giant cell tumor (TGCT), associated with severe morbidity or functional limitations and not amenable to improvement with surgery.^{7–9}

With the risk of hepatotoxicity, pexidartinib is available only through the Risk Evaluation and Mitigation Strategies (REMS) program in the United States.⁷

The pharmacokinetics (PK) of pexidartinib have been evaluated in healthy subjects and patients with TGCT or other solid tumors at doses ranging from

200 to 2400 mg.^{7,10} A pooled population PK (PopPK) analysis showed that the PK of pexidartinib in healthy subjects and patients with TGCT were similar, and that

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the multiple-dose PK of pexidartinib were predictable from single-dose data. Following a single dose of 200 or 400 mg of pexidartinib, maximum plasma concentrations (C_{\max}) were achieved at approximately 2.5 hours, with a terminal elimination half-life of approximately 25 hours.¹¹ Pexidartinib exposure, as measured by C_{\max} and the area under the plasma concentration–time curve from time 0 to infinity ($AUC_{0-\infty}$), increased in a dose-proportional manner from 200 to 400 mg, and slightly less than dose proportional from 400 to 600 mg.¹¹ ZAAD-1006 (ZAAD), a *N*-glucuronide, is the primary plasma metabolite of pexidartinib. ZAAD is minimally pharmacologically active and has approximately 10% higher systemic exposure than pexidartinib (C_{\max} and AUC) after a single dose given to healthy subjects.⁷

After oral administration of pexidartinib, approximately 65% of the administered dose is excreted in feces, with the unchanged parent drug being the primary component in feces, which could stem from unabsorbed parent drug and biliary excretion of the drug. In the ¹⁴C absorption, distribution, metabolism, and excretion (14C-ADME) study, at T_{\max} only 35% of the plasma radioactivity was associated with the parent, indicating that pexidartinib is extensively metabolized.¹² The primary metabolic pathway of pexidartinib is oxidation, via cytochrome P450 3A4 (CYP3A4) and glucuronidation, via UDP glucuronyltransferase 1A4 (UGT1A4).^{13–15} Therefore, pexidartinib exposure is affected by coadministration with a CYP3A4 inducer or inhibitor or a UGT1A4 inhibitor.⁷ Given the significant contribution of hepatic metabolism and biliary excretion of pexidartinib in elimination, and the extensive plasma protein binding of the drug (>99%), evaluating the PK of pexidartinib in subjects with mild to moderate hepatic dysfunction would be beneficial in making dose recommendations of pexidartinib in subjects with hepatic impairment (HI). As pexidartinib is extensively metabolized, there is potential that HI may lead to increased exposure of pexidartinib in HI patients.

The objective of the two phase 1, open-label studies was to determine the PK of pexidartinib after a single 200-mg dose in subjects with mild and moderate HI, based on the Child–Pugh classification (study 1) and National Cancer Institute Organ Dysfunction Working Group (NCI-ODWG; study 2) criteria, compared with healthy controls. In study 1, subjects with mild HI ($n = 8$) and moderate HI ($n = 8$) were enrolled based on Child–Pugh classification. However, following a post hoc analysis using NCI-ODWG criteria, only a limited number of subjects with moderate HI ($n = 2$) were available. In accordance with the US Food and Drug Administration (FDA)'s request, study 2 was conducted assessing the effect of moderate HI on

pexidartinib PK where hepatic dysfunction was defined by the NCI-ODWG criteria (ClinicalTrials.gov, number NCT04223635).

Methods

The Institutional Review Board at each participating center approved the study; ethics were in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines of the International Conference on Harmonisation.

Subjects

The included subjects were aged 18 to 75 years old, with a body mass index (BMI) of 18 to 40 kg/m². Female subjects of non-childbearing potential were surgically sterile for at least 6 months prior to dosing and naturally postmenopausal for at least 24 months prior to dosing. The subjects with HI had a history of chronic (>6 months) liver disease or hepatitis B virus or hepatitis C virus (HCV) infection. The hepatic impairment was defined by different criteria in the two studies.

In study 1, HI subjects were assessed by Child–Pugh score, with mild HI being defined as Child–Pugh score A (5 to 6 points) and moderate HI being defined as Child–Pugh score B (7 to 9 points). These subjects were retrospectively reclassified using the NCI-ODWG criteria. In study 2, moderate HI was assessed by NCI-ODWG criteria.¹⁶

Additionally, subjects with normal or nonclinically significant findings at physical examination, and with normal limits or nonclinically significant deviations in clinical laboratory evaluations, with the exception of findings that in the opinion of the investigator were consistent with HI, were also considered eligible.

Subjects were excluded from participation if they had primary biliary cirrhosis or primary sclerosing cholangitis, received concomitant medication (moderate or strong inhibitor or inducer of CYP3A4 [eg, itraconazole, rifampin], CYP2C9 [eg, fluconazole, carbamazepine] and uridine 5'-diphosphoglucuronosyltransferase [eg, probenecid, rifampin]) within 2 weeks before dosing and throughout the study.

Study Design and Treatment

These phase 1, nonrandomized, open-label, parallel-group, single-dose PK studies were conducted in healthy control subjects and subjects with hepatic dysfunction. Subjects were screened within 21 days of administration of the study drug, and eligible individuals were confined to the clinic starting on day –2, for approximately 10 days (Figure 1). All subjects were given a single dose of pexidartinib (1 × 200-mg capsule) orally on day 1 with 240 mL of water. Subjects fasted for at least 10 hours before pexidartinib dosing and

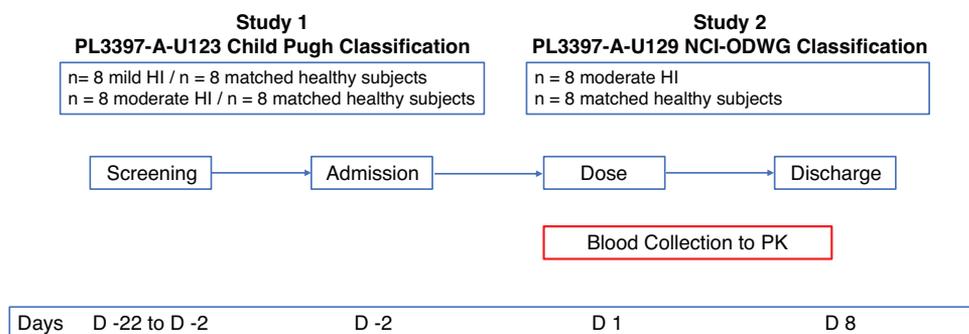


Figure 1. Study design for the PL3397-A-U123 (Child–Pugh classification) and PL3397-A-U129 (NCI-ODWG criteria) studies. D, day; HI, hepatic impairment; NCI-ODWG, National Cancer Institute Organ Dysfunction Working Group; PK, pharmacokinetics.

continued to fast for at least 4 hours after pexidartinib administration. Water was allowed ad libitum up to 1 hour prior to dosing and resumed 2 hours after pexidartinib administration.

In study 1, the severity of HI was assessed by Child–Pugh classification (graded A, B, or C), which was based on serum total bilirubin (TBIL), albumin, prothrombin time, presence of ascites, and hepatic encephalopathy. In study 2, the NCI-ODWG classification was used, with the following breakdown: mild HI (B1), TBIL \leq ULN (upper limit of normal), ALT or AST $>$ ULN; mild HI (B2), TBIL $>$ 1.0–1.5 \times ULN; moderate HI, TBIL $>$ 1.5–3.0 \times ULN (not as a result of Gilbert’s syndrome); and severe HI, TBIL $>$ 3.0 \times ULN.¹⁶ Subjects with HI were recruited first, followed by healthy matched subjects. Healthy control subjects with normal hepatic function were matched to subjects with mild HI or moderate HI according to sex, age (± 10 years), and BMI ($\text{kg}/\text{m}^2 \pm 15\%$). Of note, the 6 mild HI subjects and 23 healthy subjects based on reclassification from study 1 had similar demographic characteristics.

Study End Points

The primary end points were PK parameters of pexidartinib and ZAAD-1006a, including maximum observed concentration (C_{max}), area under the plasma concentration–time curve extrapolated to infinity (AUC_{inf}), and AUC up to the last measurable concentration (AUC_{last}). Additionally, time to maximum concentration (T_{max}) and protein binding were measured. For pexidartinib only, half-life ($t_{1/2}$), oral clearance (CL/F), and volume of distribution in the terminal phase (V_z/F) were measured, and for ZAAD-1006a only, the metabolite-to-parents ratio based on AUC_{last} was measured. Secondary end points included adverse events (AEs), vital signs, 12-lead electrocardiogram (ECG), and clinical lab tests.

Study Assessments and Parameters

Blood samples were collected for PK analysis of pexidartinib and ZAAD-1006a before dosing (within

60 minutes prior to dosing) and at 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0, 4.5, 5, 6, 8, 10, 12, 24, 36, 48, 72, 96, 120, 144, and 168 hours after dosing. Additional 10-mL samples were collected to determine protein binding at 2.5 and 24 hours after dosing.

A compartmental model-independent analysis was performed (Phoenix WinNonlin 8.1, or higher; Certara, Princeton, New Jersey) to determine PK parameters, including C_{max} , T_{max} , AUC_{last} , $t_{1/2}$, AUC_{inf} , CL/F, and V_z/F for pexidartinib, and C_{max} , T_{max} , AUC_{last} , $t_{1/2}$, and AUC_{inf} for metabolite ZAAD-1006a. The metabolite-to-parent molar ratio (MPR) of AUC_{last} was calculated for ZAAD-1006a.

The AEs were collected and reported from the time of signing the informed consent form up to 30 days after the administration of the pexidartinib dose. The intensity and relatedness of AEs were assessed using National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE, versions 4.03 and 5.0).

Bioanalytical Methods

Plasma concentrations of pexidartinib and ZAAD-1006a were determined separately by liquid chromatography tandem mass spectrometry (LC-MS/MS), developed and validated/qualified at Celerion (Lincoln, Nebraska).

The bioanalytical method utilized protein precipitation extraction and analysis using LC-MS/MS. Plasma samples (25 μL of blanks, standards, quality control [QC] samples, and study analytical samples) were aliquoted into a 2-mL 96-well plate. Internal standard (50 μL of $^{13}\text{C}_5$ -pexidartinib [100 ng/mL in 15:85 v/v acetonitrile:water] or 15:85 v/v acetonitrile:water for control blanks) was added to all samples. Following mixing, 25 μL of acetic acid (2% v/v in water) was added to each well. After mixing, 200 μL of acetonitrile was added to each well. Mixed samples were then transferred to a Zymark SciClone automated sample handling system (Caliper Life Sciences, Waltham, Massachusetts) for centrifugation at ambient temperature for

10 minutes and the removal of 100 μL of supernatant. Following the addition of 400 μL of 15:85 (v/v) acetonitrile:water to each well, samples were mixed and centrifuged for 10 minutes at 5°C. Extracted samples were analyzed on a Zorbax Bonus-RP column (Agilent, Santa Clara, California) at 50°C with a mobile phase of 30:5:65:0.05 (v/v/v/v) acetonitrile:methanol:5mM ammonium formate:heptafluorobutyric acid, at a flow rate of 0.5 mL/min. Pexidartinib and internal standard were detected using an API 4000TM triple quadrupole mass spectrometer (Sciex, Framingham, Massachusetts) using an electrospray ionization source operated under positive ionization mode.

Pexidartinib Validation

The calibration curve comprised 10 levels of nonzero pexidartinib standards, ranging from 10.0 to 5000 ng/mL. For validation of precision and accuracy, QC samples were prepared at 3 concentrations (30.0, 220, and 3750 ng/mL). Dilution integrity was verified at a concentration up to 30,000 ng/mL when diluted 20-fold and the limit of quantitation was 10.0 ng/mL. The average recovery of pexidartinib (% mean) ranged from 91% (30.0 ng/mL) to 97% (3750 ng/mL); the average recovery of the internal standard was 94%. The intra- and interbatch precision ranges (coefficient of variation, %CV) were 0.8% to 7.2% and 3.3% to 6.3%, respectively; the intra- and interbatch accuracy ranges (% bias) were -7.7% to 7.0% and -3.3% to 0.3%, respectively. The bench-top short-term stability was 24 to 26 hours in polypropylene tubes at ambient temperature under white light, whereas the cumulative short-term stability (total of all thaw cycles) was 51 to 54 hours. Freeze-thaw stability (in cycles) was 6 to 7 freeze (-20°C)-thaw (ambient temperature) cycles in polypropylene tubes under white light.

ZAAD-1006a Qualification

The calibration curve comprised 9 levels of nonzero standards, ranging from 10.0 to 5000 ng/mL. For validation of precision and accuracy, QC samples were prepared at 3 concentrations (30.0, 220, and 3800 ng/mL). Dilution integrity was verified at a concentration up to 25,000 ng/mL when diluted 10-fold and the limit of quantitation was 10.0 ng/mL. The average recovery time (% mean) ranged from 88% (30.0 ng/mL) to 92% (3800 ng/mL); the average recovery of the internal standard was 100%. The intra- and interbatch precision ranges (%CV) were 1.5% to 11.4% and 7.2% to 11.8%, respectively; the intra- and interbatch accuracy ranges (% bias) were -14.1% to 17.0% and -2.3% to 5.0%, respectively. The bench-top short-term stability was 24 hours for QCs stored at -20°C and 6 hours for QCs stored at -80°C, respectively, in polypropylene tubes

at ambient temperature under white light, whereas the cumulative short-term stability (total of all thaw cycles) was 54 hours for QCs stored at -20°C and 28 hours for QCs stored at -80°C, respectively. Freeze-thaw stability (in cycles) was 7 freeze (-20°C)-thaw (ambient temperature) cycles in polypropylene tubes under white light, and 5 freeze-thaw cycles when samples were stored at -80°C.

Statistical Analysis

Plasma concentrations of pexidartinib and ZAAD-1006a were summarized by nominal sampling times and hepatic function group using descriptive statistics, including the geometric mean, geometric coefficient of variation (%CV), and arithmetic %CV, for the PK analysis set (ie, subjects who received 1 dose of pexidartinib and had sufficient plasma concentration data). The PK parameters for pexidartinib and ZAAD-1006a were summarized by the hepatic function group using descriptive statistics. The logarithm-transformed values of C_{max} , AUC_{last} , and AUC_{inf} of pexidartinib were compared for subjects in each HI group with those of normal hepatic function in the corresponding matched control group using an analysis of variance (ANOVA) model. The resulting point estimates (geometric least-squares mean), their ratios (respective HI group/matched normal hepatic function), and 90% confidence intervals (90% CIs) for the ratios are presented for each comparison. Note, in study 1, after recategorization using the NCI-ODWG criteria, there were 6 subjects in the mild hepatic impairment (HI) group B1, 1 subject in the mild hepatic impairment group B2, 2 subjects in the moderate hepatic impairment group, and 23 subjects that would be characterized as having normal hepatic function. As there were only 2 subjects in the moderate hepatic impairment group ($n = 2$), no statistical comparison of PK data was conducted between the subjects recategorized as moderate HI and as subjects with normal hepatic function based on the NCI-ODWG criteria in study 1. Protein binding (%) was summarized by hepatic function. Treatment-emergent adverse events (TEAEs) and other safety variables were also summarized descriptively by hepatic function.

Results

Subjects

Study 1 (Child-Pugh Classification). There were 32 subjects enrolled (28 males and 4 females; median age 57 years, range 45 to 65 years) from the PL3397-A-U123 study, all of whom received a 200-mg dose of pexidartinib. The safety analysis set included all 32 subjects who received a dose of pexidartinib. Subjects with mild HI (Child-Pugh A, $n = 8$) had a mean

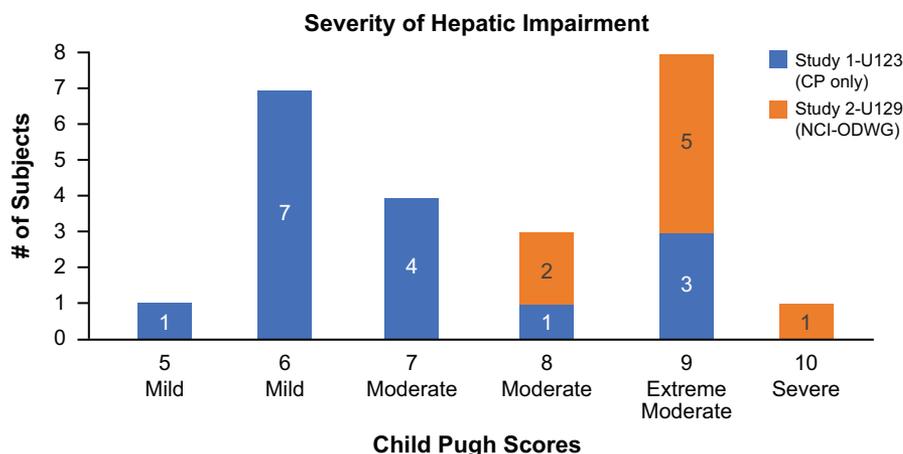


Figure 2. Breakdown of severity of hepatic impairment based on Child–Pugh classification (blue) versus National Cancer Institute Organ Dysfunction Working Group criteria (orange). CP, Child–Pugh; NCI-ODWG, National Cancer Institute Organ Dysfunction Working Group.

score of 5.9 and subjects with moderate HI (Child–Pugh B, $n = 8$) had a mean score of 7.9. There were 16 healthy subjects with normal hepatic function: 8 matched healthy controls for each hepatic impaired group (Figure 1). Of the 8 patients with mild HI, 1 (13%) had a Child–Pugh score of 5, and 7 (87%) had a score of 6. Of the 8 patients with moderate HI, 4 (50%) had a score of 7, and 1 (13%) and 3 (37%) had scores of 8 and 9, respectively. Most subjects were male (28/32, 88%), with a median age of 56.5 years (Figure 2; Table S1). When the 16 patients with HI were reclassified using the NCI-ODWG criteria, 7 were considered to have normal hepatic function and the remaining 9 patients with HI were classified as 7 with mild HI (6 B1 and 1 B2) and 2 with moderate HI.

Study 2: NCI-ODWG Criteria. A total of 16 subjects (8 with moderate HI and 8 matched healthy controls; 10 males and 6 females; with a mean age of 59 years, range 49 to 69 years) were enrolled. When the 8 subjects with moderate HI (based on NCI-ODWG criteria) were reclassified by Child–Pugh score, 2 (25%) had a score of 8, 5 (63%) had a score of 9, and 1 (13%) had a score of 10 (severe HI; Child–Pugh C), respectively (Figure 1). The subjects with moderate HI based on NCI-ODWG had a numerically higher mean Child–Pugh score (8.9), and were therefore considered to have more severe hepatic impairment, as compared with the subjects enrolled with moderate HI based on the Child–Pugh scores used in study 1 (7.9) (Figure 2; Table S1).

Pharmacokinetic Analyses

As the HI was defined by both Child–Pugh and NCI-ODWG criteria, for each analyte (pexidartinib and ZAAD-1006a) the results are presented as grouped by the definition criteria within each HI class, instead of by study. Subjects with mild HI were from study 1 only,

whereas subjects with moderate HI were from both study 1 (Child–Pugh score) and study 2 (NCI-ODWG criteria).

Effect of Mild Hepatic Impairment on Pexidartinib Pharmacokinetics

Child–Pugh Score. Exposure to pexidartinib after oral administration (200 mg) was similar for subjects with mild HI and the corresponding subjects with normal hepatic function. The mean pexidartinib C_{max} was slightly lower in subjects with mild HI (1650 ng/mL) compared with healthy control subjects with normal hepatic function (1910 ng/mL) (Figure 3; Table 1), whereas the mean AUC_{last} (mild HI, 30 500 ng·h/mL, versus matching controls, 29 900 ng·h/mL) and AUC_{inf} (mild HI, 31 500 ng·h/mL, versus matching controls, 30 800 ng·h/mL) were similar across these 2 groups (Table 1). A small difference was noted in the T_{max} comparing subjects with mild HI (median, 1.5 hours) against healthy control subjects with normal hepatic function (median, 2.25 hours), whereas $t_{1/2}$ (29.3 hours vs 27.6 hours) was similar across the groups with mild HI and healthy controls, respectively (Table 1). Mean CL/F (7.1 L/h vs 8.1 L/h) and V_z/F (290.5 L vs 292.7 L) were similar between subjects with mild HI and healthy control subjects (Table S2).

From the ANOVA analysis (mean geometric least-squares ratio), a 12% decrease in C_{max} (1449 ng/mL vs 1655 ng/mL) and an approximate 8% increase in AUC values (AUC_{last} , 29 010 ng·h/mL vs 26 810 ng·h/mL; AUC_{inf} , 29 989 ng·h/mL vs 27 641 ng·h/mL) was observed in subjects with mild HI; however, the 90% CIs of the C_{max} and AUC values were wide, and included 1.0 (Table 2).

NCI-ODWG Criteria. The pexidartinib mean C_{max} in subjects with mild HI (B1, $n = 6$) was numerically

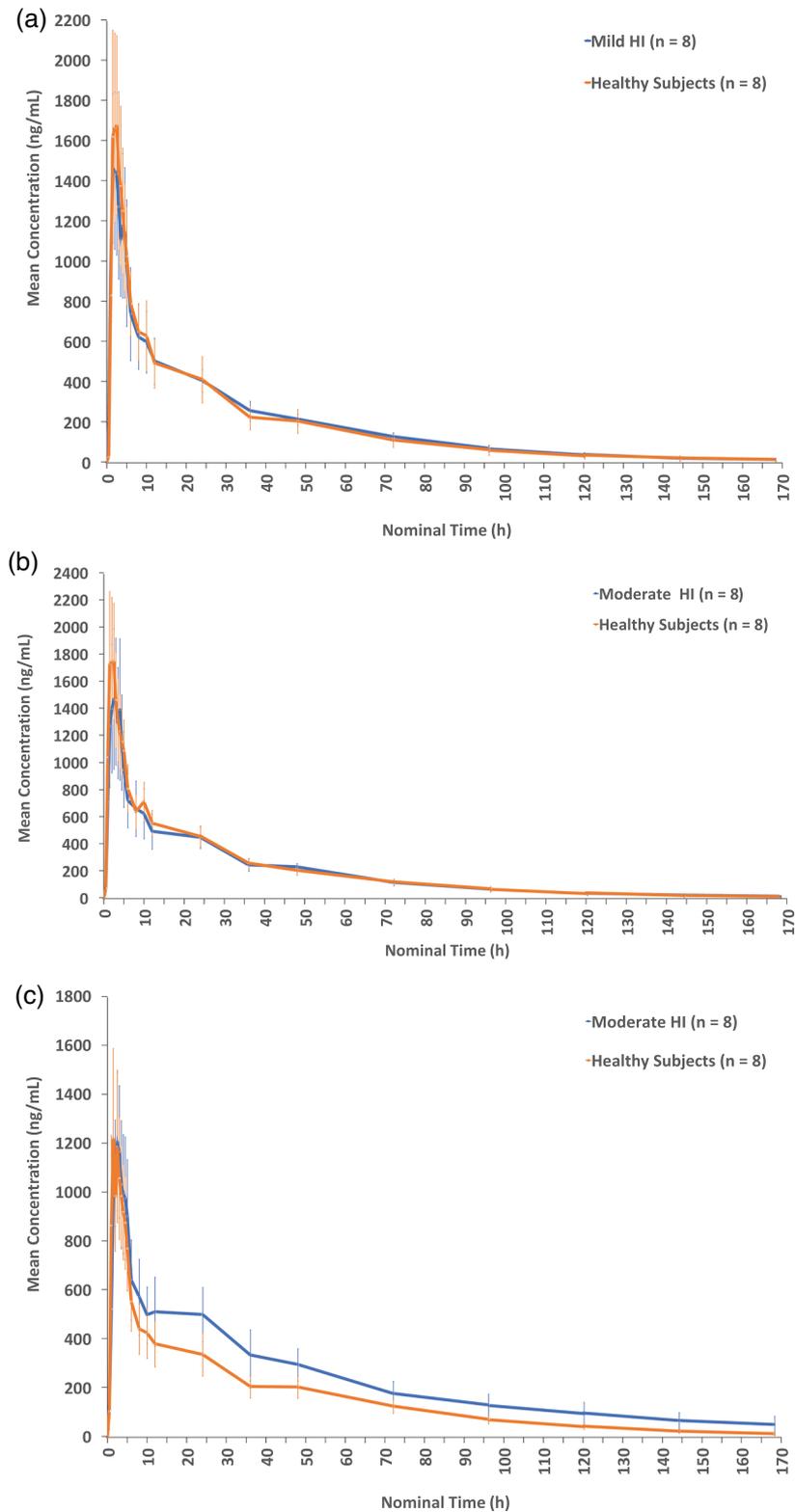


Figure 3. Mean (SD) plasma pexidartinib concentrations in subjects with (a) mild hepatic impairment (Child–Pugh A) and moderate hepatic impairment by (b) Child–Pugh B and (c) NCI-ODWG, plotted in blue, versus subjects with normal hepatic function, plotted in orange, on a linear scale. h, hour; HI, hepatic impairment; NCI-ODWG, National Cancer Institute Organ Dysfunction Working Group.

Table 1. Plasma Pharmacokinetic Parameters of Pexidartinib in Patients With Mild and Moderate Hepatic Impairment, Compared With Matched Healthy Controls Based on Child–Pugh Classification and NCI-ODWG Criteria

HI Classification/Parameter	Mild HI and Matching Healthy Control			Moderate HI and Matching Healthy Control		
	n	Mild HI	Matching Healthy Control	n	Moderate HI	Matching Healthy Control
Child–Pugh						
Study 1 (PL3397-A-U123)						
C_{max} (ng/mL)	8	1650 (773)	1910 (1040)	8	1910 (1160)	1970 (971)
Arithmetic mean (SD)						
T_{max} (h)	8	1.50 (1.00, 2.50)	2.25 (1.50, 6.00)	8	2.5 (1.00, 4.00)	2 (1.50, 2.50)
Median (min, max)						
AUC_{last} (ng·h/mL)	8	30 500 (9470)	29 900 (14 700)	8	30 800 (8950)	32 200 (11 100)
Arithmetic mean (SD)						
AUC_{inf} (ng·h/mL)	8	31 500 (9560)	30 800 (15 200)	8	32 300 (n = 7) (9170)	33 100 (11 600)
Arithmetic mean (SD)						
$t_{1/2}$ (h)	8	29.3 (11.4)	27.6 (10.1)	8	24.1 (n = 7) (4.89)	27.7 (7.56)
Arithmetic mean (SD)						
NCI-ODWG						
Study 1 (Reclassified)						
C_{max} (ng/mL)	6	2110 (902)	1790 (947) (n = 23) ^a	8	1250 (556)	1420 (738)
Arithmetic mean (SD)						
T_{max} (h)	6	2.5 (1.50, 4.00)	1.5 (1.00, 6.00) (n = 23) ^a	8	2.5 (2.00, 3.00)	1.88 (1.50, 4.50)
Median (min, max)						
AUC_{last} (ng·h/mL)	6	33 200 (6900)	30 100 (11 500) (n = 23) ^a	8	38 600 (16 200)	26 500 (12 200)
Arithmetic mean (SD)						
AUC_{inf} (ng·h/mL)	6	34 300 (6900)	31 200 (12 100) (n = 23) ^a	7	38 900 (17 600)	27 300 (12 400)
Arithmetic mean (SD)						
$t_{1/2}$	6	29.0 (10.7)	27.4 (8.6) (n = 23) ^a	7	36.5 (8.1)	30.4 (2.6)
Arithmetic mean (SD)						

AUC_{inf} , area under the plasma concentration–time curve from time of dosing extrapolated to infinity; AUC_{last} , area under the plasma concentration–time curve from time 0 to the time of the last quantifiable measurement; CI, confidence interval; C_{max} , maximum observed plasma concentration; h, hour; HI, hepatic impairment; n, number of subjects; NCI-ODWG, National Cancer Institute Organ Dysfunction Working Group; SD, standard deviation; $t_{1/2}$, terminal elimination half-life; T_{max} , time to reach maximum concentration.

^aThe 23 subjects reclassified as having normal hepatic function based on NCI-ODWG are not matched controls.

higher (2110 ng/mL vs 1790 ng/mL) compared with healthy control subjects with normal hepatic function. Both AUC_{last} (33 200 ng·h/mL vs 30 100 ng·h/mL) and AUC_{inf} (34 300 ng·h/mL vs 31 200 ng·h/mL) were similar for subjects with mild HI compared with healthy control subjects with normal hepatic function. Furthermore, the mean $t_{1/2}$ was similar among the patients with mild HI (29.0 hours) compared with healthy controls with normal hepatic function (27.4 hours) (Table 1).

From the ANOVA analysis (mean geometric least-squares ratio), a 27% increase in C_{max} (1942 ng/mL vs 1531 ng/mL) and a 17% increase in AUC values (AUC_{last} , 32 663 ng·h/mL vs 28 000 ng·h/mL; AUC_{inf} , 33 735 ng·h/mL vs 28,965 ng·h/mL) was observed in subjects with mild HI; however, the 90% CIs of the C_{max} and AUC values were wide, and included 1.0 (Table 2). High plasma protein binding (99.96% to 99.97%) of pexidartinib was observed, irrespective of the hepatic function group (mild HI vs matched healthy controls) and plasma concentrations.

Effect of Moderate Hepatic Impairment on Pharmacokinetics of Pexidartinib

Child–Pugh Score. The mean pexidartinib C_{max} was similar in subjects with moderate HI (1910 ng/mL) and healthy controls with normal hepatic function (1970 ng/mL) (Figure 3; Table 1). In addition, the mean AUC_{last} (moderate HI, 30 800 ng·h/mL, vs matching healthy controls, 32 200 ng·h/mL) and AUC_{inf} (moderate HI, 32 300 ng·h/mL, vs matching healthy controls, 33 100 ng·h/mL) were similar across these 2 groups (Table 1). A small difference was noted in the T_{max} comparing subjects with moderate HI (median, 2.5 hours) against healthy control subjects with normal hepatic function (median, 2.0 hours), whereas $t_{1/2}$ (24.1 hours vs 27.7 hours) was similar across the moderate HI and healthy control subject groups, respectively (Table 1). Mean CL/F (6.6 L/h vs 6.7 L/h) and V_z/F (229.9 L vs 256.1 L) were similar between subjects with moderate HI and healthy control subjects (Table S2).

Subjects with moderate HI had similar exposure compared with healthy control subjects. The mean

Table 2. Statistical Analysis of the Pharmacokinetic Parameters of Pexidartinib in Patients With Mild Hepatic Impairment and Matched Healthy Control Subjects With Normal Hepatic Function

PK Parameter (Unit)	Child–Pugh Classification Study 1 (PL3397-A-U123)			NCI-ODWG Study 1 (Reclassified)		
	Matched Healthy		Ratio of LS Means (90%CI) ^a	Matched Healthy		Ratio of LS Means (90%CI) ^a
	Mild HI n = 8	Controls n = 8		Mild HI n = 6	Healthy Controls ^b n = 23	
C _{max} (ng/mL)	1449	1655	87.6 (51.7, 148)	1942	1531	126.8 (80.7, 199.4)
AUC _{last} (ng·h/mL)	29 010	26 810	108 (73.6, 159)	32 663	28 000	116.7 (87.4, 155.6)
AUC _{inf} (ng·h/mL)	29 989	27 641	109 (73.8, 160)	33 735	28 965	116.5 (86.7, 156.4)

The model was performed on logarithm-transformed PK parameters including the study group as a factor. The geometric LS means presented are LS means from the model with back-transformation to the original scale.

AUC_{inf}, area under the plasma concentration–time curve from time of dosing extrapolated to infinity; AUC_{last}, area under the plasma concentration–time curve from time 0 to the time of the last quantifiable measurement; CI, confidence interval; C_{max}, maximum observed plasma concentration; h, hour; HI, hepatic impairment; LS, least squares; n, number of subjects; NCI-ODWG, National Cancer Institute Organ Dysfunction Working Group; Normal, normal hepatic function; PK, pharmacokinetics.

^aRatio = geometric LS mean (mild/moderate)/geometric LS mean (normal). The 90%CI are presented after back-transformation to the original scale. Expressed as percent (compared with 100%).

^bHealthy control subjects were pooled into 1 category; some of the HI subjects from study 1 were reclassified as healthy subjects based on NCI-ODWG criteria.

Table 3. Statistical Analysis of the Pharmacokinetic Parameters of Pexidartinib in Patients With Moderate Hepatic Impairment and Matched Healthy Control Subjects With Normal Hepatic Function

PK Parameter (Unit) Pexidartinib	Child–Pugh Classification Study 1 (PL3397-A-U123)			NCI-ODWG Study 2 (PL3397-A-U129)		
	Matched Healthy		Ratio of LS Means (90%CI) ^a	Matched Healthy		Ratio of LS Means (90%CI) ^a
	Moderate HI n = 8	Controls n = 8		Moderate HI n = 8	Controls n = 8	
C _{max} (ng/mL)	1566	1722	91.0 (51.3, 161.2)	1121	1211	92.6 (54.4, 157.7)
AUC _{last} (ng·h/mL)	29 777	30 534	97.5 (73.7, 129.1)	35 276	23 969	147.2 (95.4, 227.1)
AUC _{inf} (ng·h/mL)	31 212	31 341	99.6 (74.0, 134)	35 421 (n = 7)	24 793	142.9 (91.2, 223.8)

The model was performed on logarithm-transformed PK parameters including the study group as a factor. The geometric LS means presented are LS means from the model with back-transformation to the original scale.

AUC_{inf}, area under the plasma concentration–time curve from time of dosing extrapolated to infinity; AUC_{last}, area under the plasma concentration–time curve from time 0 to the time of the last quantifiable measurement; CI, confidence interval; C_{max}, maximum observed plasma concentration; h, hour; HI, hepatic impairment; LS, least squares; n, number of subjects; NCI-ODWG, National Cancer Institute Organ Dysfunction Working Group; Normal, normal hepatic function; PK, pharmacokinetics.

^aRatio = geometric LS mean (mild/moderate)/geometric LS mean (normal). The 90%CI are presented after back-transformation to the original scale. Expressed as percent (compared with 100%).

pexidartinib C_{max} values in subjects with moderate HI and healthy control subjects were 1566 ng/mL and 1722 ng/mL, respectively. Comparing the moderate HI group with the healthy control group, the AUC_{last} values were 29 777 ng·h/mL and 30 534 ng·h/mL, respectively, and the AUC_{inf} values were 31 212 ng·h/mL and 31 341 ng·h/mL, respectively (Table 3).

NCI-ODWG Criteria. The maximum pexidartinib exposure (C_{max}) was similar for subjects with moderate HI (1250 ng/mL) compared against matched healthy control subjects with normal hepatic function (1420 ng/mL). The median T_{max} was similar for both populations (moderate HI, 2.50 hours; healthy subjects, 1.88 hours) (Figure 3). Total pexidartinib exposure (AUC_{last} and AUC_{inf}) was 46% (38 600 ng·h/mL vs

26 500 ng·h/mL) and 42% (38 900 ng·h/mL vs 27 300 ng·h/mL) higher in subjects with moderate HI compared with healthy control subjects. The mean t_{1/2} was approximately 6 hours longer for subjects with moderate HI (36.5 hours) compared with healthy control subjects (30.4 hours) (Table 1). The mean plasma protein binding of pexidartinib was 99.97% for both populations (subjects with moderate HI vs healthy matched controls). Of note, for the two patients who were retrospectively classified as having moderate HI from study 1, the maximum pexidartinib exposure (C_{max}) was similar for subjects with moderate HI (1940 ng/mL, n = 2) compared with reclassified healthy control subjects with normal hepatic function (1790 ng/mL, n = 23). The median T_{max} was longer for subjects with moderate HI (3.25 hours) compared with

reclassified healthy subjects (1.50 hours). Total pexidartinib exposure (AUC_{last} and AUC_{inf}) was similar (33 300 ng·h/mL, $n = 2$, vs 30 100 ng·h/mL, $n = 23$) and (33 700 ng·h/mL, $n = 2$, versus 31 200 ng·h/mL, $n = 23$), respectively, in subjects with moderate HI compared with reclassified healthy control subjects. The mean $t_{1/2}$ was shorter for subjects with moderate HI (19.9 hours, $n = 2$) compared with reclassified healthy controls (27.4 hours, $n = 23$).

From the ANOVA analysis (mean geometric least-squares ratio), a 7% decrease in C_{max} (1121 ng/mL vs 1211 ng/mL) and an approximate 47% increase in AUC values (AUC_{last} , 35 276 ng·h/mL vs 23 969 ng·h/mL; AUC_{inf} , 35 421 ng·h/mL vs 24 793 ng·h/mL) was observed in subjects with moderate HI; however, the 90% CIs of the C_{max} and AUC values were wide and included 1.0 (Table 3).

Within the moderate HI group as defined by the NCI-ODWG criteria, there was one subject who had been defined as having severe HI by the Child–Pugh score. Pexidartinib exposure in this subject was relatively lower than in the other subjects ($n = 7$) of this group (Figure S1). These limited data indicate that possibly within the subgroup of population (moderate HI) defined by NCI-ODWG there is no trend in exposure by Child–Pugh score.

Effect of Mild Hepatic Impairment on Pharmacokinetics of ZAAD-1006a

Child–Pugh Score. The mean concentration time profile of ZAAD-1006a was slightly higher numerically in subjects with mild HI and the respective matched healthy controls (Figure 4). The mean ZAAD-1006a C_{max} was similar for subjects with mild HI (1650 ng/mL) compared against healthy control subjects with normal hepatic function (1780 ng/mL), and was observed slightly later in the mild HI group (median T_{max} 4.75 hours vs 3.00 hours). AUC_{last} and AUC_{inf} were 27% (61 500 ng·h/mL vs 48 400 ng·h/mL) and 28% (63 500 ng·h/mL vs 49 800 ng·h/mL) higher, respectively, for subjects with mild HI compared with the healthy control group. The metabolite-to-parent molar ratio was also numerically higher in the mild HI group compared with the healthy control group (1.42 vs 1.19) (Table 4).

NCI-ODWG Criteria. The mean ZAAD-1006a C_{max} was 49% higher for subjects with mild HI ($n = 6$, B1; 2420 ng/mL) compared against healthy control subjects with normal hepatic function ($n = 23$, 1620 ng/mL), and was observed slightly later in the mild HI group (median T_{max} 4.75 hours vs 4.00 hours). AUC_{last} (84 700 ng·h/mL vs 46 900 ng·h/mL) was 81% higher and AUC_{inf} (86 900 ng·h/mL vs 48 500 ng·h/mL) was 79% higher for subjects with mild HI compared with

the healthy control group (Table 4). The metabolite-to-parent molar ratio was also numerically higher in the mild HI group compared with the healthy control group (1.86 vs 1.15) (Table 4).

Effect of Moderate Hepatic Impairment on the Pharmacokinetics of ZAAD-1006a

Child–Pugh Score. ZAAD-1006a exposure was numerically higher in subjects with moderate hepatic impairment. The mean ZAAD-1006a C_{max} was 16% higher (1960 ng/mL vs 1690 ng/mL), and the median T_{max} was observed later (4.50 hours vs 3.75 hours) for subjects with moderate HI compared with the healthy control group (Figure 4). AUC_{last} and AUC_{inf} were 41% higher (67 400 ng·h/mL vs 47 700 ng·h/mL) and 48% higher (72 300 ng·h/mL vs 48 700 ng·h/mL), respectively, in the moderate HI group (Table 4). The metabolite-to-parent molar ratio was 42% higher (1.55 vs 1.09) in the moderate HI group (Table 4). Plasma protein binding of pexidartinib was similar (mean protein binding >99.96%) in subjects with normal hepatic function and in subjects with mild to moderate HI.

NCI-ODWG Criteria. The C_{max} for ZAAD-1006a was 27% lower (1250 ng/mL vs 1720 ng/mL) in subjects with moderate HI. The total ZAAD-1006a exposure (AUC_{last} and AUC_{inf}) was 70% higher (72 700 ng·h/mL vs 42 700 ng·h/mL) and 79% higher (78 100 ng·h/mL vs 43 700 ng·h/mL) for subjects with moderate HI compared against matched healthy control subjects with normal hepatic function (Figure 4; Table 4). The median T_{max} was approximately 7 hours later for subjects with moderate HI (10.0 hours) compared with healthy matched subjects (3.0 hours). The mean $t_{1/2}$ was approximately 9 hours longer (37.9 hours vs 28.9 hours) and metabolite-to-parent ratios (MPRs) were slightly higher numerically (AUC_{last} , 19%, 1.30 vs 1.09 [Table 4]; AUC_{inf} , 25%, 1.35 vs 1.08) for subjects with moderate HI compared with healthy control subjects. The mean plasma protein binding of ZAAD-1006a was 99.86% for both subject populations. Of note, for the 2 patients who were retrospectively classified as having moderate HI from study 1, the maximum ZAAD-1006a exposure (C_{max}) was similar for subjects with moderate HI (2020 ng/mL, $n = 2$) compared with reclassified healthy control subjects with normal hepatic function (1620 ng/mL, $n = 23$). The median T_{max} was longer for subjects with moderate HI (7.25 hours) compared with reclassified healthy subjects (4.00 hours). Total pexidartinib exposure (AUC_{last} and AUC_{inf}) was 61% higher (75 300 ng·h/mL, $n = 2$, vs 46 900 ng·h/mL, $n = 23$) and 56% higher (75 800 ng·h/mL, $n = 2$, vs 48 500 ng·h/mL, $n = 23$), respectively, in subjects with moderate HI compared with reclassified healthy control subjects. The mean $t_{1/2}$ was similar for subjects with moderate HI

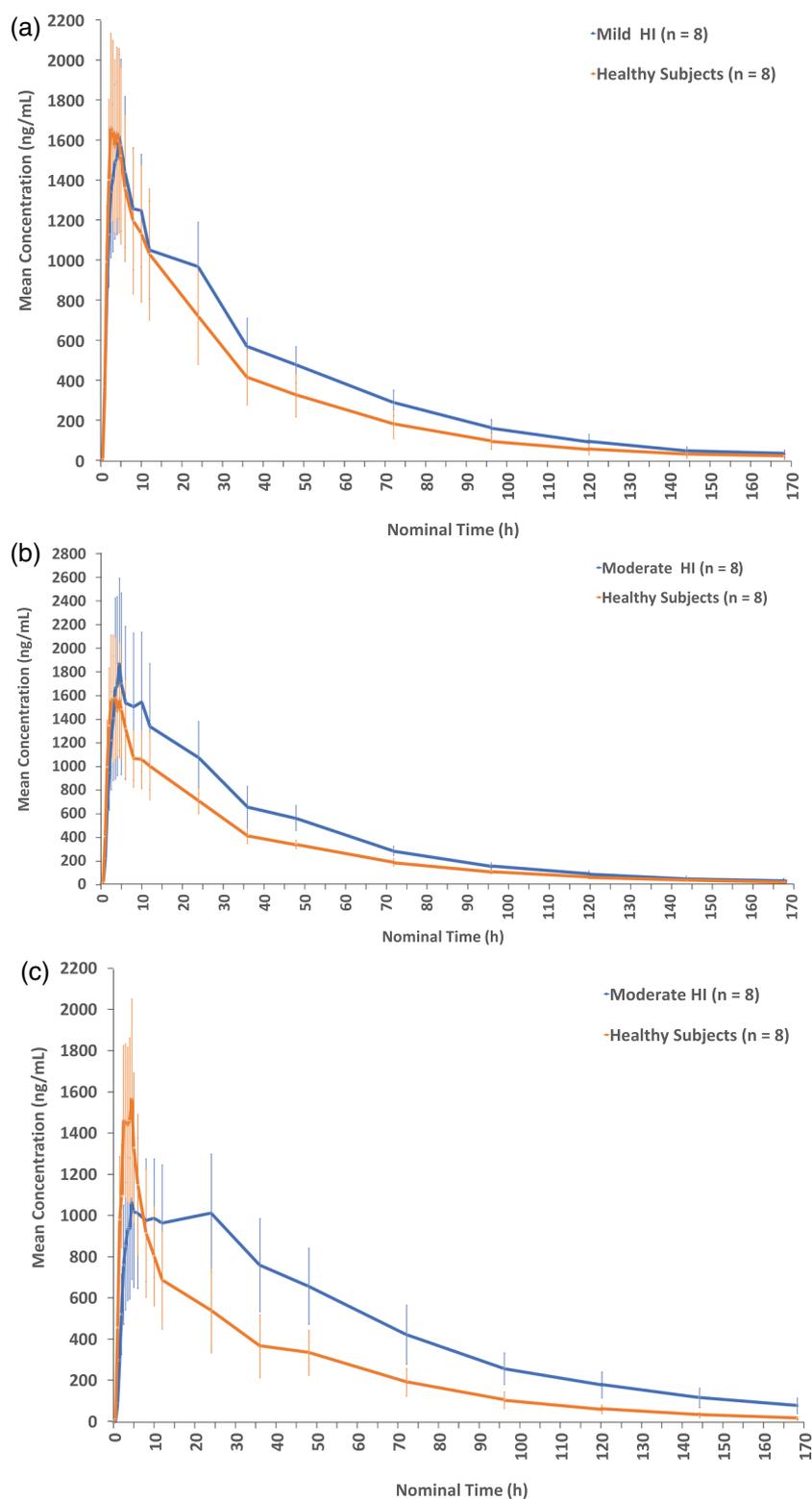


Figure 4. Mean (SD) plasma ZAAD-1006a concentrations in subjects with (a) mild hepatic impairment (Child–Pugh A) and moderate hepatic impairment by (b) Child–Pugh B and (c) NCI-ODWG, plotted in blue, versus subjects with normal hepatic function, plotted in orange, on a linear scale. h, hour; HI, hepatic impairment; NCI-ODWG, National Cancer Institute Organ Dysfunction Working Group.

Table 4. Plasma Pharmacokinetic Parameters of ZAAD-1006a in Patients With Mild and Moderate Hepatic Impairment Compared With Matched Healthy Controls Based on Child–Pugh Classification and NCI-ODWG Criteria

HI Classification/Parameter	Mild HI and Matching Healthy Control			Moderate HI and Matching Healthy Control		
	n	Mild HI	Matched Healthy Control	n	Moderate HI	Matched Healthy Control
Child–Pugh						
Study 1 (PL3397-A-U123)						
C_{max} (ng/mL)	8	1650 (834)	1780 (895)	8	1960 (1550)	1690 (1050)
Arithmetic mean (SD)						
T_{max} (h)	8	4.75 (2.50, 10.00)	3.00 (2.50, 6.00)	8	4.50 (2.50, 10.00)	3.75 (2.50, 10.00)
Median (min, max)						
AUC_{last} (ng·h/mL)	8	61 500 (24 000)	48 400 (30 300)	8	67 400 (30 200)	47 700 (16 900)
Arithmetic mean (SD)						
AUC_{inf} (ng·h/mL)	8	63 500 (24 800)	49 800 (31 500)	8	72 300 (n = 7) (30 000)	48 700 (17 100)
Arithmetic mean (SD)						
MPR AUC_{last}	8	1.42 (0.34)	1.19 (0.54)	8	1.55 (0.63)	1.09 (0.34)
Arithmetic mean (SD)						
NCI-ODWG						
Study 1 (Reclassified)						
C_{max} (ng/mL)	6	2420 (n = 6) (1430)	1620 (n = 23) (886)	8	1250 (766)	1720 (950)
Arithmetic mean (SD)						
T_{max} (h)	6	4.75 (n = 6) (4.5, 10.0)	4.00 (n = 23) (2.5, 10.0)	8	10.0 (4.50, 8.50)	3.0 (2.50, 4.50)
Median (min, max)						
AUC_{last} (ng·h/mL)	6	84 700 (n = 6) (15 600)	46 900 (n = 23) (20 500)	8	72 700 (36 900)	42 700 (28 800)
Arithmetic mean (SD)						
AUC_{inf} (ng·h/mL)	6	86 900 (n = 6) (15 000)	48 500 (n = 23) (21 500)	8	78 100 (38 300)	43 700 (29 300)
Arithmetic mean (SD)						
MPR AUC_{last}	6	1.86 (n = 6) (0.57)	1.15 (n = 23) (0.39)	8	1.30 (0.37)	1.09 (0.28)
Arithmetic mean (SD)						

AUC_{inf} , area under the plasma concentration–time curve from time of dosing extrapolated to infinity; AUC_{last} , area under the plasma concentration–time curve from time 0 to the time of the last quantifiable measurement; CI, confidence interval; C_{max} , maximum observed plasma concentration; h, hour; HI, hepatic impairment; MPR, metabolite-to-parent ratio (molecular-weight corrected); n, number of subjects; NCI-ODWG, National Cancer Institute Organ Dysfunction Working Group; SD, standard deviation; $t_{1/2}$, terminal elimination half-life; T_{max} , time to reach maximum concentration.

MPR = metabolite-to-parent ratio based on AUC_{last} was corrected for molecular weight using the following formula: (ZAAD-1006a AUC_{last} /593.94)/(pexidartinib AUC_{last} /417.82).

Normal subjects were pooled into I category (n = 23).

(1.5 hours, n = 2) compared with reclassified healthy control subjects (1.15 hours, n = 23).

As observed with pexidartinib exposure, the single subject defined as having severe HI by the Child–Pugh score had a relatively lower ZAAD-1006a exposure than was observed for the other subjects (n = 7) in this group (Figure S2).

Safety

Regarding the number of TEAEs reported, 7 of 32 (22%) subjects classified by Child–Pugh score experienced TEAEs (all grade 1 or 2): 4 were in subjects with mild HI, 2 were in subjects with moderate HI, and 1 was in a subject with healthy to mild HI. Of these, the TEAEs reported by 3/32 (9%) subjects were assessed as being related to the study drug, and were of grade 1 (dyspepsia, moderate HI; headache, mild HI) or grade 2 (increased and AST, mild HI) intensity, as assessed by the investigator. For subjects classified by NCI-ODWG criteria (n = 16), 3 (19%) reported TEAEs (2 in subjects with moderate HI [conjunctival hemorrhage,

grade 1; dyspepsia, grade 2]; 1 in a healthy matched subject [headache, grade 1]). None of the TEAEs were treatment related. From both studies, no subject was discontinued or withdrawn as a result of a TEAE. No deaths or serious adverse event (SAEs) were reported. No clinically significant abnormal hematology or coagulation, or clinically relevant changes in vital signs, ECGs, or physical exams were reported.

Discussion

This is the first analysis to characterize the effect of hepatic impairment on pexidartinib and ZAAD-1006a in subjects with hepatic impairment, with the goal to support pexidartinib labeling and dosing in subgroups of patients of interest. Following the oral administration of 200 mg pexidartinib to subjects with mild and moderate HI, and their respective healthy control subjects with normal hepatic function, exposure to pexidartinib was similar in subjects with mild HI, irrespective of the classification used to define the

hepatic impairment (Child–Pugh or NCI-ODWG criteria), and in their respective healthy control subjects with normal hepatic function. Therefore, pexidartinib can be administered without any dose modifications in this population. Subjects with moderate HI as defined by Child–Pugh score did not have any effect on pexidartinib PK. In contrast, total pexidartinib exposure (AUC_{last} and AUC_{inf}) was approximately 40% to 50% higher in subjects with moderate HI as defined by the NCI-ODWG criteria compared with matched healthy control subjects.

The mean ZAAD-1006a C_{max} was similar for subjects with mild HI and normal hepatic function and was numerically higher for subjects with moderate HI classified by Child–Pugh score, but was numerically lower for subjects with moderate HI classified by NCI-ODWG criteria, compared with the matched controls. The peak levels were observed slightly later in both the mild and moderate HI groups. In subjects classified by Child–Pugh scores, AUC values for ZAAD-1006a were 40% to 50% higher for subjects with mild and moderate HI, compared with the control group. The impact of moderate HI on the AUC of ZAAD-1006a was even greater (70% higher for moderate HI subjects) when subjects were classified based on NCI-ODWG criteria. The metabolite-to-parent ratios were numerically higher in patients with moderate HI classified by Child–Pugh and NCI-ODWG criteria. In humans, pexidartinib is mainly metabolized by CYP3A4 and UGT1A4. In subjects with hepatic impairment, CYP3A activity decreases with increases in hepatic dysfunction. On the contrary, according to the literature, in subjects with hepatic impairment there is increased UGT activity in the viable part of the liver and upregulation of the extrahepatic UGTs.¹⁵ The increased exposure of ZAAD-1006a may result from an increased generation of the metabolite linked to a higher concentration of circulating parent drug, and probably through increased UGT activity in the viable part of the liver or upregulation of the extrahepatic UGTs.¹⁷

High plasma protein binding (>99%) of pexidartinib and ZAAD-1006a was observed, irrespective of the subject population (HI subjects vs matched healthy controls) and extent of HI (mild HI or moderate HI).

With chronic dosing at doses of 800 to 1000 mg/day, pexidartinib has been associated with clinically distinct hepatic adverse reactions, including serious and potentially fatal mixed or cholestatic hepatotoxicity, all of which were reversible in patients with TGCT.^{18–20} In the current studies, a single dose of 200 mg pexidartinib was well tolerated and demonstrated a safety profile consistent with previous findings. All reported TEAEs from both studies were of grades 1 or 2. Based on Child–Pugh classification ($n = 32$), 7 subjects (22%) experienced TEAEs (4 with mild HI, 2 with moderate

HI, 1 with healthy to mild HI). Of these TEAEs, 3 were treatment related. For subjects classified by NCI-ODWG criteria, 3/16 (19%) reported TEAEs (2 with moderate HI, 1 healthy matched subject); none were treatment related.

No dosage adjustment is recommended for patients with mild hepatic impairment (with total bilirubin less than or equal to upper limit of normal [ULN] and with AST greater than ULN or total bilirubin greater than 1.0 to 1.5 times ULN with any AST).⁷ A reduced dose of 200 mg twice daily is recommended for patients with moderate hepatic impairment, as defined by NCI-ODWG criteria (TBIL greater than 1.5 and up to 3.0 times ULN, not linked to Gilbert's syndrome, with any AST). This analysis indicated approximately a 40% increase in pexidartinib exposure following administration in subjects with moderate HI, as defined by NCI-ODWG criteria. The PK of pexidartinib is linear from 200 to 2400 mg, and pexidartinib is currently only available in a 200 mg capsule. Therefore, to maintain pexidartinib exposure at the same level as that observed in subjects with normal hepatic function using the current available dose strength, a 50% dose reduction was proposed. The observed difference in the effect of moderate HI on pexidartinib PK in the 2 HI studies (study 1 based on Child–Pugh classification and study 2 based on NCI-ODWG criteria) probably results from the difference in the extent of HI within the study population, particularly with regards to moderate HI. The distribution of Child–Pugh score for subjects with moderate HI in study 1 versus study 2 indicated that the frequency of subjects with higher Child–Pugh score was greater in study 2 (Figure 2). This finding is consistent with literature data indicating that NCI-ODWG includes subjects with a relatively greater extent of HI, as compared with the Child–Pugh score.

Limitations

Initially, subjects were enrolled in study 1 based on the Child–Pugh classification, as recommended in the FDA guidance for industry “Pharmacokinetics in Patients with Impaired Hepatic Function: Study Design, Data Analysis, and Impact on Dosing and Labeling.” However, after recategorization using the NCI-ODWG criteria,^{16,21} there were 7 subjects in the mild hepatic impairment group (HI; B1 and B2; 8 with mild HI according to Child–Pugh classification), 2 subjects in the moderate hepatic impairment group (8 according to Child–Pugh classification), and 7 subjects that would be characterized as having normal hepatic function. As there were only 2 subjects in total in the moderate hepatic impairment group, no statistical comparison of PK data was conducted between this group and subjects with normal hepatic function. To address this limitation, the U129 study includes 8 subjects with

moderate HI, as defined by NCI-ODWG criteria, and their 8 healthy control subjects.

Conclusions

No dose modification of pexidartinib is needed for mild hepatic impairment. However, the recommended dosage of pexidartinib for patients with moderate HI (TBIL greater than 1.5 and up to 3 times ULN, not linked to Gilbert's syndrome, with any AST) is reduced to 200 mg twice daily instead of 400 mg twice daily. Overall, the results of these studies guided the dosing recommendation of pexidartinib in subjects with hepatic impairment.

Conflicts of Interest

H.Z. reports employment with and support for study-related travel from Daiichi Sankyo, Inc., during the time of the study. J.C. reports employment with and stock in Daiichi Sankyo, Inc. C.H. reports employment and stock in Daiichi Sankyo, Inc. T.C.M. and K.C.L. have no potential conflicts of interest to disclose. L.-A.X. reports employment with and stock and stock options in Daiichi Sankyo, Inc. W.D.T. reports consulting fees and honoraria from Kowa Research Institute, Ayala Pharmaceuticals, Inc., Medpacto, Servier, Novo Holdings, MundiBioPharma, AmMax Bio, C4 Therapeutics, Deciphera, Blueprint, Nano Carrier, EMD Serono, Agios, Daiichi Sankyo, GSK, Eli Lilly, Medscape, Agios, Epizyme, Inc. (Nexus Global Group), Bayer, Cogent Biosciences, Amgen, and Aadi Biosciences; patent and royalties or license from Companion Diagnostics for CDK4 inhibitors (14/854,329); participation on Data Safety Monitoring Board or Advisory Board for C4 Therapeutics, Blueprint, GSK, and MundiBioPharma; leadership or fiduciary role with Osteosarcoma Institute (OSI) and Sarcoma Foundation of America (SFA); stock or stock options in Certis Oncology Solutions and Atropos. J.H.H. reports consulting fees from Daiichi Sankyo, Inc., and Stryker, and participation on Data Safety Monitoring Board or Advisory Board for Daiichi Sankyo, Inc. S.S. reports: funding for the present study from Daiichi; grants to her institution from Advenchen, Amgen Dompè, Bayer, Daiichi Sankyo, Deciphera, Epizyme, Eli Lilly, Glaxo, Karyopharm, Novartis, Pfizer, Pharmamar, and Springworks; honoraria from Aadi, Glaxo, RainThera, and Pharmamar; support for attending meetings and travel from Pharmamar; participation on Data Safety Monitoring Board or Advisory Board for Bavarian Nordic, Pharmamar, Glaxo, Bayer, Daiichi, Epizyme, Maxivax, Novartis, Ikena; and unpaid leadership or fiduciary role in Italian Sarcoma Group, ESMO, Connective Tissue Oncology Society, EORTC, Chordoma Foundation, Desmoid Foundation, Epithelioid Hemoendothelioma Foundation. F.L. reports employment with and stock and stock options in Daiichi Sankyo, Inc.

Data Sharing

De-identified individual participant data (IPD) and applicable supporting clinical trial documents may be made available, upon request, at <https://www.clinicalstudydatarequest.com//>. In cases where clinical trial data and supporting documents are provided pursuant to our company policies and procedures, Daiichi Sankyo, Inc., will continue to protect the privacy of our clinical trial 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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Supplemental Information

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