CLINICAL STUDY PROTOCOL

AN OPEN-LABEL, SINGLE-DOSE STUDY TO ASSESS THE PHARMACOKINETICS OF PEXIDARTINIB IN SUBJECTS WITH MODERATE HEPATIC IMPAIRMENT COMPARED TO HEALTHY SUBJECTS

PL3397-A-U129

IND 105521

VERSION 2.0, 10 DEC 2019

VERSION 1.0, 23 OCT 2019

DAIICHI SANKYO, INC.
211 MT. AIRY ROAD
BASKING RIDGE, NJ 07920

PL3397-A-U129 Protocol
Version 2.0, 10 DEC 2019

INVESTIGATOR AGREEMENT

AN OPEN-LABEL, SINGLE-DOSE STUDY TO ASSESS THE PHARMACOKINETICS OF PEXIDARTINIB IN SUBJECTS WITH MODERATE HEPATIC IMPAIRMENT COMPARED TO HEALTHY SUBJECTS

Sponsor Approval:

This clinical study protocol has been reviewed and approved by the Daiichi Sankyo, Inc. representative listed below.

PPD	PPD
Print Name	**Signature**
Clinical Study Leader	10 Dec 2019
Title	**Date (DD MMM YYYY)**

Investigator's Signature:

I have fully discussed the objectives of this study and the contents of this protocol with the Sponsor's representative.

I understand that information contained in or pertaining to this protocol is confidential and should not be disclosed, other than to those directly involved in the execution or the ethical review of the study, without written authorization from the Sponsor. It is, however, permissible to provide information to a subject in order to obtain consent.

I agree to conduct this study according to this protocol and to comply with its requirements, subject to ethical and safety considerations and guidelines, and to conduct the study in accordance with the Declaration of Helsinki ICH E6, and applicable regional regulatory requirements.

I agree to make available to Sponsor personnel, their representatives and relevant regulatory authorities, my subjects' study records in order to verify the data that I have entered into the case report forms. I am aware of my responsibilities as Principal Investigator as provided by the Sponsor.

I understand that the Sponsor may decide to suspend or prematurely terminate the study at any time for whatever reason; such a decision will be communicated to me in writing. Conversely, should I decide to withdraw from execution of the study, I will communicate my intention immediately in writing to the Sponsor.

PPD	PPD
Print Name	**Signature**
Principal Investigator	12 - Dec - 2019
Title	**Date (DD MMM YYYY)**

Investigator's Signature:

I have fully discussed the objectives of this study and the contents of this protocol with the Sponsor's representative.

I understand that information contained in or pertaining to this protocol is confidential and should not be disclosed, other than to those directly involved in the execution or the ethical review of the study, without written authorization from the Sponsor. It is, however, permissible to provide information to a subject in order to obtain consent.

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PPD	PPD
Print Name	**Signature**
P. I	19 DEC 2019
Title	**Date (DD MMM YYYY)**

PL3397-A-U129 Protocol
Version 2.0, 10 DEC 2019

SUMMARY OF CHANGES

Rationale:

Changes were made to the protocol in response to comments from the Food and Drug Administration (FDA).

Changes to the Protocol:

The summary of changes below is a top-line summary and rationale of significant changes to Version 1.0 of the PL3397-A-U129 clinical study protocol by section.

DESCRIPTION OF EACH HIGH-LEVEL CHANGE	
Sections	**Change**
Section 4.1 Inclusion Criteria	As advised by the FDA, the following criterion was added to the list of inclusion criteria: "Creatinine Clearance ≥ 70 mL/min estimated using the Cockcroft Gault formula without any markers of chronic kidney disease at Screening and Check-in."
Section 4.2 Exclusion Criteria	The following criterion #8 was deleted from the list of exclusion criteria: "Estimated glomerular filtration rate <70 mL/min by Cockroft-Gault equation at Screening and Check-in"

PL3397-A-U129 Protocol
Version 2.0, 10 DEC 2019

PROTOCOL SYNOPSIS

EudraCT:	Not applicable
IND Number:	105521
Protocol Number:	PL3397-A-U129
Investigational Medicinal Product:	Pexidartinib Hydrochloride (HCl) (PLX3397 HCl) capsules (200 mg)
Active Ingredient:	Pexidartinib (PLX3397)
Study Title:	An Open-label, Single-dose Study to Assess the Pharmacokinetics of Pexidartinib in Subjects with Moderate Hepatic Impairment Compared to Healthy Subjects
Study Phase:	Phase 1
Indication Under Investigation:	Not applicable
Study Rationale	Following a single dose of 200 mg pexidartinib, exposure was not affected by mild and moderate hepatic impairment (HI) (as defined by Child-Pugh criteria) (PL3397-A-U123). However, following reanalysis of the data by categorizing the HI subjects using National Cancer Institute Organ Dysfunction Working Group (NCI-ODWG) criteria for hepatic impairment, only 1 subject was identified with moderate HI. Therefore, the current study has been designed to investigate the effect of moderate HI as defined by the NCI-ODWG criteria on the pharmacokinetics (PK) of pexidartinib. In this study, HI will be assessed by (NCI-ODWG) criteria which is based on total bilirubin (TBIL) and aspartate aminotransferase (AST), as compared to Child-Pugh which uses a composite score of TBIL, prothrombin time, presence of ascites, and hepatic encephalopathy.
Study Objectives	**Primary Objective** To determine the plasma pharmacokinetics (PK) of pexidartinib after a single oral dose of 200 mg in subjects with moderate HI compared to that in healthy subjects with normal hepatic function. **Secondary Objectives** • To assess the safety and tolerability of pexidartinib after a single oral dose of 200 mg in subjects with normal and moderately impaired hepatic function

	• To determine the PK of ZAAD-1006a in subjects with moderate HI, compared to that in healthy subjects with normal hepatic function • To assess protein binding of pexidartinib and ZAAD-1006a in subjects with moderate HI, compared to that in healthy subjects with normal hepatic function.
Study Design:	This is a Phase 1, open-label, single dose PK study in male and female subjects with normal and moderately impaired hepatic function. The study will consist of 8 subjects with moderate HI and matched controls (8 healthy subjects with normal hepatic function). The severity of HI will be assessed by the NCI-ODWG criteria to identify subjects with moderate HI for enrollment in this study. The cohort of subjects with normal hepatic function will be group matched to subjects with moderate HI according to sex, age (± 10 years [y]), and weight (± 20%) based on mean values. Subjects with moderate HI will be recruited first. Healthy subjects with normal hepatic function will be enrolled after all moderate HI subjects have received study drug. Subjects will be screened within 21 days (d) prior to the administration of study drug. Subjects will be admitted to the clinical unit on Day -2 and will remain domiciled until the completion of all study procedures approximately 168 hours (h) after oral administration of 200 mg pexidartinib (1 × 200-mg capsule). Study drug will be administered on Day 1 in the morning following an overnight fast of 10 h. Water consumption will be restricted from 1 h predose to 2 h post dose, except for the specified amount that is to be administered with study drug. Fasting will continue until 4 h after study drug administration. Serial blood samples will be collected for PK analysis of pexidartinib and ZAAD-1006a at predose (within 30 minutes [min] prior to dosing) and at 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 8, 10, 12, 24, 36, 48, 72, 96, 120, 144, and 168 h post dose. Plasma will be harvested and analyzed for the quantification of pexidartinib using a validated liquid chromatography-tandem mass spectrometry method. ZAAD-1006a will be analyzed using a qualified liquid chromatography-tandem mass spectrometry assay.

	A complete physical examination will be performed at Screening, Check-in, and Check-out or Early Termination (ET). Clinical chemistry panel, hematology, urinalysis, and coagulation tests will be performed at Screening, Check-in, at 48 h and 120 h post dose, and at Check-out or ET. Single 12-lead electrocardiograms (ECGs) and vital signs will be performed at Screening, Check-in, Day 1 (predose [at least 60 min prior to pexidartinib dosing], and at 1, 2, 3 and 4 h post dose), at Check-out or ET. Adverse events (AEs) and prior/concomitant medications will be monitored and recorded throughout the study.
Study Duration:	Screening will occur within 21 d of Check-in (Day -2) at the clinic. The duration of the study for each individual subject will be approximately 5 weeks (wk) from the start of Screening (within 21 d of dosing) through the End-of-Study.
Study Sites and Locations:	The study will be conducted at up to 3 sites.
Subject Eligibility Criteria:	Screening: Male and female subjects, 18 y to 75 y of age, inclusive, with body mass index (BMI) 18 kg/m^2 to 40 kg/m^2, inclusive at Screening. Subjects with HI are required to have: • Documented history of chronic liver disease diagnosed by ultrasonography, computed tomography scan, liver biopsy, or magnetic resonance imaging or history of chronic (>6 months) hepatitis B virus or hepatitis C virus infection. • Moderate HI as assessed by the National Cancer Institute-Organ Dysfunction Working Group (NCI-ODWG) criteria (total bilirubin [TBIL] >1.5 to 3x upper limit of normal [ULN]) not due to Gilbert's syndrome. • Normal or nonclinically relevant findings at physical examination and normal limits or nonclinically relevant deviations in clinical laboratory evaluations, with exception of findings that in the opinion of investigator are consistent with subject's HI. • Clinical stability in the opinion of the investigator.

	• Female subjects (both, healthy and HI subjects) who are of non-childbearing potential must be: – Surgically sterile (ie, bilateral tubal ligation or removal of both ovaries and/or uterus at least 6 mo prior to dosing, or Essure® with hysterosalpingogram [documentation to confirm tubal occlusion 12 wk after procedure]). – Naturally postmenopausal (spontaneous cessation of menses) for at least 12 consecutive mo prior to dosing, confirmed by follicle stimulating hormone (FSH) or estradiol testing. • Female subjects (both, healthy and HI subjects) who are of childbearing potential must agree to barrier method of contraceptive therapy or refrain from sexual intercourse to prevent pregnancy until 1 mo post dose. If the subject is on oral contraceptive, the subject needs to use the barrier method in addition to oral contraceptive. Female subjects must refrain from breastfeeding for at least 2 weeks post dose. • Male subjects (both, healthy and HI subjects) must surgically sterile or agree to use double barrier methods of contraception from Check-in until 1 mo after the dose of pexidartinib. Also, male subjects must not donate sperm from Check-in until 1 mo after pexidartinib administration.
Dosage Form, Dose, and Route of Administration:	Pexidartinib 1 × 200-mg capsule will be administered orally on Day 1 with 240 mL of water, following an overnight fast of at least 10 h.
Study Endpoints:	**Pharmacokinetic Endpoints** • Pexidartinib: Cmax, Tmax, AUClast, AUCinf, kel, t1/2, CL/F, Vz/F and degree of plasma protein binding. • The following PK parameters of ZAAD-1006a will be calculated: Cmax, Tmax, AUClast, AUCinf, t1/2, degree of plasma protein binding

	and metabolite to parent ratio (MPR) for AUClast and AUCinf. **Safety Endpoints** Pexidartinib safety and tolerability will be assessed by: • AEs • Vital signs • 12-lead ECGs • Clinical laboratory tests
Planned Sample Size:	Sixteen subjects will be enrolled; 8 will have moderate HI and 8 will be healthy subjects with normal hepatic function who are group matched to subjects in the HI group by age, sex, and body weight.
Statistical Analyses:	**Pharmacokinetics:** Descriptive statistics by population (moderate HI and healthy subjects with normal hepatic function) will be presented for pexidartinib and ZAAD-1006a plasma concentrations at each time point and for all PK parameters of pexidartinib and ZAAD-1006a for both total and unbound plasma concentrations. Cmax, AUClast, and AUCinf of pexidartinib (based on total and unbound concentrations) will be compared between subjects in the HI group and subjects in the matched control group with normal hepatic function. These comparisons will be made using an analysis of variance model. The resulting point estimates (geometric least squares means), their ratios (HI/normal hepatic function), and 90% confidence intervals (CIs) for the ratios will be presented. **Safety:** The number and percentage of subjects reporting treatment-emergent adverse events (TEAEs) will be tabulated by Medical Dictionary for Regulatory Activities (MedDRA) system organ class and preferred term, for each group and the overall study. ECG interval measurements and other safety endpoints will be summarized using descriptive statistics when appropriate.

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LIST OF ABBREVIATIONS

ABBREVIATION	DEFINITION
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
AUCinf	area under the concentration-time curve up to infinity
AUClast	area under the concentration-time curve up to the last measurable time point
BMI	body mass index
CI	confidence interval
CL/F	total apparent clearance
Cmax	maximum concentration
CRO	Contract Research Organization
CSF-1	colony stimulating factor-1
CSF1R	receptor of CSF-1 and interleukin 34
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P450
d	day(s)
DBP	diastolic blood pressure
DSI	Daiichi Sankyo, Inc.
ECG	electrocardiogram
eCRF	electronic Case Report Form
EDC	electronic data capture
EIU	exposure in utero
EoS	End of Study
ET	Early Termination
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GGT	Gamma-glutamyl transferase

ABBREVIATION	DEFINITION
h	hour(s)
HAV	hepatitis A virus
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HI	hepatic impairment
HIV	human immunodeficiency virus
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IMP	investigational medicinal product
INR	International Normalized Ratio
IRB	Institutional Review Board
kel	Elimination rate constant
MedDRA	Medical Dictionary for Regulatory Activities
min	minute(s)
mo	month(s)
MPR	metabolite to parent ratio after adjusting for molecular weight
ms	millisecond(s)
NCI-ODWG	National Cancer Institute Organ Dysfunction Working Group
NDA	New Drug Application
OTC	over-the-counter
PK	pharmacokinetic
PT	prothrombin time
QTcB	QT interval corrected for heart rate using Bazett's formula
QTcF	QT interval corrected for heart rate using Fridericia's formula
SAE	serious adverse event
SAP	Statistical Analysis Plan
SAVER	Serious Adverse Event Report

ABBREVIATION	DEFINITION
SBP	systolic blood pressure
SOC	system organ class
SUSAR	Suspected Unexpected Serious Adverse Reaction
t1/2	terminal elimination half-life
TBIL	total bilirubin
TEAE	treatment-emergent adverse event
TGCT	tenosynovial giant cell tumor
UGT	uridine 5'-diphospho-glucuronosyltransferase
ULN	Upper limit of normal
US	United States
Vz/F	volume of distribution in the terminal phase
WHO	World Health Organization
wk	week(s)
y	year(s)

1. INTRODUCTION

1.1. Background

Pexidartinib is a novel, orally administered, small-molecule tyrosine kinase inhibitor that targets the receptor for colony stimulating factor-1 (CSF-1) and interleukin 34 (CSF1R), Kit (the receptor for stem cell factor), and oncogenic Flt3 (the receptor for Flt3 ligand), but it remains highly selective compared to other tyrosine kinase inhibitors. The potent inhibition of these kinases can be exploited to attack tumors via different mechanisms: 1) directly inhibiting oncogenic drivers, such as oncogenic Kit and Flt3 mutant proteins, 2) inhibiting paracrine loops between stromal cells and tumors, 3) blocking migration and angiogenesis, and 4) disrupting osteolytic metastases.[1] CSF-1 and its receptor CSF1R have been shown to play a role in a rare connective tissue neoplasia known as pigmented villonodular synovitis, more recently termed tenosynovial giant cell tumor (TGCT).[2] This disease is generally characterized by hypersecretion of CSF-1 as a result of translocations within synovial cells linking the CSF-1 and the collagen COL6A3 genes. The resulting tumor cells overexpress CSF-1, which leads to the recruitment of CSF1R-expressing monocytes and macrophages. Indeed, the pigment that characterizes the tumor mass is derived primarily from hemosiderin-laden macrophages. The strong genetic link between TGCT and CSF-1/CSF1R provides a solid scientific rationale for the use of pexidartinib in the treatment of TGCT, as a therapy targeting the underlying genetic defect.

As of 31 Jul 2018, pexidartinib has been evaluated in 28 company-sponsored clinical studies in healthy subjects and in patient populations (cancer and TGCT).

Seven studies in patient populations have been completed: Study PLX108-03 in subjects with relapsed or refractory Hodgkin's lymphoma, Study PLX108-04 in subjects with recurrent glioblastoma multiforme (GBM), Study PLX108-05 in subjects with relapsed or refractory FLT3-ITD-positive acute myeloid leukemia (AML), Study PLX108-06 in subjects with advanced metastatic prostate cancer, Study PLX108-07 in subjects with advanced solid tumors treated with PLX3397 and paclitaxel, Study PLX108-08 in subjects with newly diagnosed glioblastoma, and Study PLX108-09 pexidartinib in combination with vemurafenib in v-Raf murine sarcoma viral oncogene homolog B (BRAF)-mutated unresectable or metastatic melanoma. There were 6 ongoing studies in patient populations, of which 5 were Phase 1 or Phase 1/2 studies (PLX108-01, PLX108-13, PLX108-14, PL3397-A-A103, and PLX121-01) and 1 was a Phase 3 study (PLX108-10). Across these studies, 645 subjects with cancer or TGCT were treated with pexidartinib and were assessed for safety and efficacy.

Fifteen clinical pharmacology studies were completed or are ongoing. Fourteen single-dose studies were completed in healthy subjects, including 2 studies in subjects with renal or hepatic impairment along with healthy subjects (PL3397-A-U124 and PL3397-A-U123, respectively). In the completed clinical pharmacology studies, a total of 338 subjects were treated with pexidartinib. One multiple-dose study in subjects is currently ongoing (PL3397-A-U126); these subjects were not included in the total number of subjects treated.

In addition, 6 investigator-initiated studies evaluating pexidartinib are ongoing.

1.2. Data Summary

Detailed nonclinical and clinical information can be found in the Investigator's Brochure (IB).[1]

The current FDA approved Prescribing Information for pexidartinib (Turalio™) is attached.[3]

1.2.1. Overview of Biopharmaceutics

Pexidartinib is administered as a 200 mg capsule strength with multiple capsules being given to achieve the target daily dose of 800 mg (2 × 200 mg capsules twice daily). Following oral administration, pexidartinib exposure increased dose proportionally over the dose range of 200 mg to 2400 mg. Due to the relatively large food effect (doubling of exposure when administered with a high fat meal), pexidartinib is recommended to be taken on an empty stomach at least 1 hour before or 2 hours after a meal.

Coadministration of pexidartinib with a systemic gastric pH modifier, esomeprazole, resulted in an approximate 50% decreased exposure of pexidartinib irrespective of the capsule formulation used (Study PLX108-11 and Study PL3397-A-U120), presumably due to decreased solubility leading to reduced absorption of pexidartinib with an increase in gastric pH. Consistent with the decreased exposure of the parent, ZAAD-1006a exposure was also decreased by approximately 50% resulting in a similar metabolite to parent molar ratio (MPR) between the treatments consistent with the conclusion of a decrease in pexidartinib absorption with an increase in gastric pH.

Overall, the biopharmaceutics of pexidartinib have been well characterized.

For additional information refer to the Investigator Brochure Version 10.0, 19 DEC 2018.

1.2.2. Overview of Clinical Pharmacology

A comprehensive series of clinical (N=14) studies and analyses have been conducted to elucidate the PK of pexidartinib and the impact of intrinsic (e.g. renal function, gastric pH) and extrinsic factors (e.g. food, concomitant administration with strong CYP3A4 inducers/inhibitors, UGT inhibitors, gastric acid lowering agents) on the exposure of pexidartinib. In all cases, the nonclinical study results were aligned with and supported the clinical study results, and the integrated analyses were consistent with the individual studies.

In Study PL3397-A-U123, pexidartinib PK was not affected by mild and moderate hepatic impairment (HI), as defined by Child-Pugh criteria, compared to subjects with normal hepatic function. There was however, an increase in ZAAD-1006a AUC (up to approximately 50%) and MPR (up to about 40%).

Subsequently, additional analysis was conducted by recategorizing the HI subjects using NCI-ODWG criteria[4]. Based on this recategorization only 1 subject with moderate hepatic impairment was identified. Therefore, the current study has been designed. The USPI provides dosing recommendations for patients with mild hepatic impairment.

1.2.3. Clinical Experience

The pexidartinib clinical development program, up to the New Drug Application (NDA) cutoff date of 31 Jan 2018, comprised 28 completed or ongoing studies sponsored by Daiichi Sankyo, Inc. (DSI), or its subsidiary Plexxikon Inc.

In most clinical pharmacology studies, a single 600mg dose of pexidartinib was administered in the fasted state and resulted in mean Cmax and AUC of approximately 6000 ng/mL and 110,000 ng•h/mL, respectively (PL3397-U117). The highest exposure of pexidartinib was observed at 1800 mg administered with a high-fat meal (Cmax: 20,800 ng/mL AUC: 491,948 ng•h/mL). In the fasted state, pexidartinib exposure increases with dose in an approximate dose proportional manner. In general, ZAAD-1006a was present at approximately 110% of parent exposure (Cmax and AUC) and with an elimination t1/2 similar to that of pexidartinib. Based on the dosing interval and elimination t1/2 of pexidartinib, accumulation of parent with repeated administration is expected to be about 2-fold compared to the first dose.

Although the findings from study PL3397-A-U123 demonstrated mild and moderate HI, as assessed by the Child-Pugh criteria, does not affect pexidartinib exposure, compared to healthy subjects, the vast majority of subjects with moderate HI did not meet the NCI-ODWG criteria for moderate HI, which is based on total bilirubin (TBIL). In healthy subjects, single doses up to 2400 mg (with or without food) were well-tolerated. Aside from minor gastrointestinal side effects, no safety signals in vital signs, physical examinations, or electrocardiograms (ECGs) were reported following up to 3 single doses of pexidartinib administered with a subject across multiple studies. [1, 5]

Based on pooled data from the clinical studies in patients, the most frequent adverse events (AEs) (occurring in >10% of subjects) potentially related to study drug were fatigue, nausea, decreased appetite, hair color changes, diarrhea, aspartate aminotransferase (AST) / alanine aminotransferase (ALT) increases, vomiting, anemia, dysgeusia, and rash. Among all common treatment-related treatment-emergent adverse events (TEAEs), fatigue, increased AST/ALT, anemia, and rash occurred at Grade 3 or higher severity and at a frequency greater than 1%. At dosage levels ≥600 mg/d, transient increases in AST and/or ALT have been commonly observed with repeated dosing.[1] Mild to moderate (Grade 1 to 2) increases in aminotransferases have been found in about 50% of subjects treated with pexidartinib alone or in combination. These findings may be related to target inhibition of CSF1R in the Kupffer cells that are responsible for clearing transaminases that leak from hepatocytes. Single doses up to 2600 mg have been administered to subjects with cancer. Among common TEAEs, fatigue, increased AST and ALT levels, anemia, and rash occurred at Grade 3 or higher severity and at a frequency greater than 1%.[1]

Elevations of liver transaminases and bilirubin have been observed in studies with pexidartinib, together with cases of drug induced cholestatic liver injury following multiple doses. Cases of cholestasis have been observed in the first 8 wk, have generally resolved with treatment discontinuation, but in some cases have been severe, requiring liver dialysis and had a protracted course (8 months [mo]).

1.3. Study Rationale

Given the significant contribution of hepatic metabolism and biliary excretion of pexidartinib in humans, findings from Study PL3397-A-U123 demonstrated mild and moderate HI, as assessed

by the Child-Pugh criteria, do not affect pexidartinib exposure, compared to healthy subjects. Because the vast majority of subjects with moderate HI as defined by Child-Pugh in the first study did not meet the NCI-ODWG criteria for hepatic dysfunction, which is based on, TBIL another study is being conducted to further define the effect of moderate HI on the PK of pexidartinib. Findings from this study will be useful in making dose recommendations in patients with moderate HI who would benefit from pexidartinib.

The current (Turalio™ USPI-TUR-08919-r001) FDA product labeling states that no dosage adjustment is recommended for patients with mild hepatic impairment (TBIL ≤ ULN with AST > ULN or TBIL > 1 to 1.5 X ULN with any AST. Also, the current FDA product labeling states that the recommended dose of Turalio™ has not been established for patients with moderate (TBIL > 1.5 to 3 X ULN and any AST) to severe (TBIL >3 X ULN and any AST) hepatic impairment.

1.4. Risks and Benefits for Study Subjects

There is no direct benefit for subjects in the current study. Indirect benefits to the healthy subjects enrolled in this study are the free medical tests received during Screening and the safety monitoring as mandated by the study.

The PK, safety, and tolerability of single doses of pexidartinib (200 mg to 2400 mg) in approximately 190 healthy subjects has been evaluated in 9 studies. In general, pexidartinib was well-tolerated up to average peak exposure of 20,800 ng/mL and a total exposure (based on AUC) of 491,948 ng•h/mL (1800 mg fed state). No safety signals in vital signs, physical examinations, or ECG recordings, including QT prolongation, were reported.[1] Assuming a 50% decrease in hepatic metabolism and biliary excretion of pexidartinib in subjects with moderate HI, the exposure from a 200-mg dose would not be expected to exceed that observed following an 1800-mg dose administered with food in healthy subjects (eg, 4- to 6-fold difference in Cmax and AUC). Therefore, the risk for uncovering a new untoward effect of a single dose of pexidartinib is relatively small.

Based on pooled data from the oncology studies with multiple dosing, the most frequent AEs (occurring in >10% of subjects) potentially related to the study drug were fatigue, nausea, decreased appetite, hair color changes, diarrhea, increases in AST and ALT levels, vomiting, anemia, dysgeusia, and rash. At dosage levels ≥ 600 mg/d, transient increases in AST and/or ALT levels have been commonly observed with multiple dosing. Among common TEAEs, fatigue, increased AST and ALT levels, anemia, and rash were rated Grade 3 or higher with a frequency >1%.[1]

Elevations of liver transaminases and bilirubin have been observed in studies with pexidartinib, together with cases of drug induced cholestatic liver injury following multiple doses. Cases of cholestasis have been observed in the first 8 wk, have generally resolved with treatment discontinuation, but in some cases have been severe, requiring liver dialysis and had a protracted course (8 mo) (Turalio™ Full Prescribing Information).[3]

2. STUDY OBJECTIVES AND HYPOTHESIS

2.1. Study Objectives

2.1.1. Primary Objective

The primary objective of this study is:

- To determine the plasma PK of pexidartinib after a single oral dose of 200 mg in subjects with moderate HI compared to that in healthy subjects with normal hepatic function

2.1.2. Secondary Objectives

The secondary objectives of this study are:

- To assess the safety and tolerability of pexidartinib after a single oral dose of 200 mg in subjects with normal and moderately impaired hepatic function
- To determine the PK of ZAAD-1006a in subjects with moderate HI, compared to that in healthy subjects with normal hepatic function
- To assess protein binding of pexidartinib and ZAAD-1006a in moderate HI, compared to that in healthy subjects with normal hepatic function

2.2. Study Hypothesis

This is not a hypothesis testing study. This study will estimate the effect of moderate hepatic dysfunction on the PK of pexidartinib and ZAAD-1006a, compared to a group of healthy subjects with normal hepatic function.

2.3. Study Endpoints

2.3.1. Primary Endpoints

Pharmacokinetic Endpoints

- Pexidartinib: Plasma Cmax, Tmax, AUClast, AUCinf, Kel, t1/2, CL/F, Vz/F, and protein binding
- ZAAD-1006a: Plasma Cmax, Tmax, AUClast, AUCinf, t1/2, MPR based on AUClast and AUCinf, and protein binding

The following unbound PK parameters will be calculated for both pexidartinib and ZAAD 1006a:

- Cmax
- Tmax
- AUClast
- AUCinf

- t1/2

And also for pexidartinib:

- CL/F
- Vz/F

2.3.2. Secondary Endpoints

Safety Endpoints

- AEs
- Vital signs
- 12-lead ECGs
- Clinical laboratory tests

2.3.3. Exploratory Endpoint

Not applicable

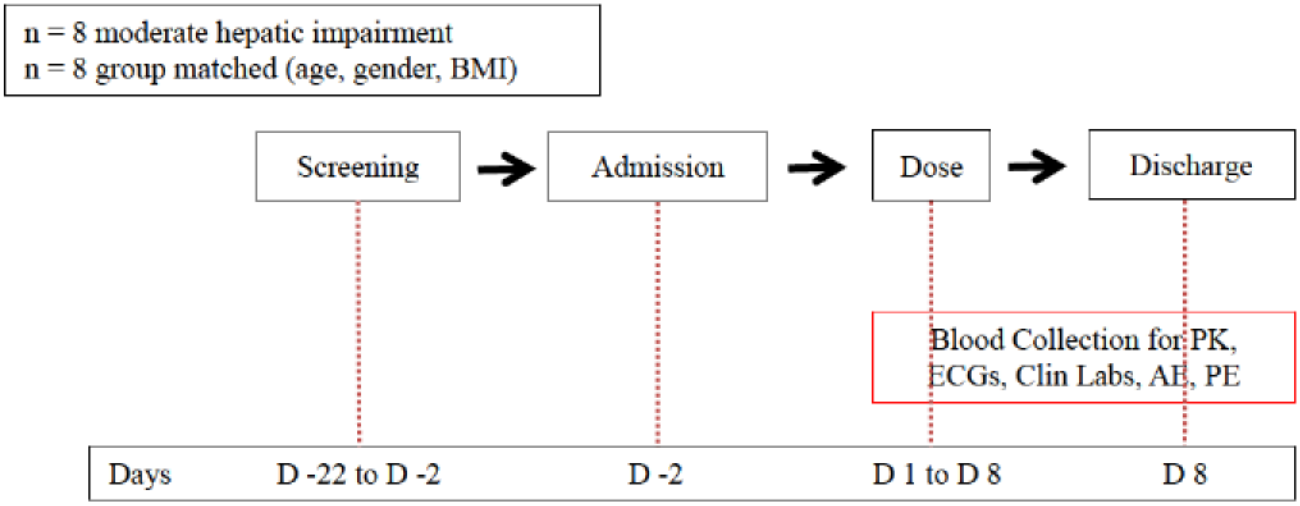
3. STUDY DESIGN

3.1. Overall Design

3.1.1. Overview

This is a Phase 1, open-label, 1-treatment, 1-period study conducted in healthy subjects with normal hepatic function and in subjects with moderate hepatic impairment. An overview of the study is depicted in Figure 3.1 below:

Figure 3.1: Overview of study design



Abbreviations: D = Day; PK = pharmacokinetics

Screening will occur within 21 d of Check-in (Day -2) at the clinic, and eligible individuals will be confined at the clinic starting on Day -2 for approximately 8 d. All subjects will be given a single dose of pexidartinib (1 × 200-mg capsule) orally on Day 1 with 240 mL of water. Subjects will fast for at least 10 h before pexidartinib dosing and will continue to fast for at least 4 h after pexidartinib administration. Water will be allowed ad libitum up to 1 h prior to dosing and resuming at 2 h after pexidartinib administration.

Subjects will check out from the clinic on Day 8 of the study following completion of the final blood collection and Check-out procedures.

Details for each study visit are provided in the study procedures section (see Section 6) and the Schedule of Events table (see Appendix 16.5).

3.1.2. Dose Escalation Process

Not applicable

3.1.3. Study Stopping Criteria

Not applicable

3.2. Discussion of Study Design

The purpose of this study is to assess the effect of moderate HI on the PK of pexidartinib. The study will consist of 8 subjects with moderate HI and 8 matched controls. The severity of HI will be assessed by the NCI-ODWG group TBIL >1.5 to 3x ULN, not due to Gilbert's syndrome. Subjects with normal hepatic function will be matched to subjects with moderate HI according to sex, age (± 10 years [y]), and weight (± 20%) based on mean values. Subjects with HI will be recruited first. Healthy subjects with normal liver function will be enrolled after all subjects with moderate HI have received study drug.

A single 200-mg dose of pexidartinib (1 × 200-mg capsule) was chosen based on the safety profile and with an assumption that moderate hepatic impairment may double the exposure. The open-label, single dose study design is appropriate for this Phase 1 study.

4. STUDY POPULATION

All subjects must sign an Informed Consent Form (ICF) provided by the site.

4.1. Inclusion Criteria

Subjects must satisfy all of the following criteria to be included in the study:

1. Male and female subjects 18 y to 75 y of age (inclusive), with a body mass index (BMI) of 18 kg/m^2 to 40 kg/m^2 (inclusive) at Screening.
2. Female subjects who are of non-childbearing potential must be:
   a. Surgically sterile (ie, bilateral tubal ligation or removal of both ovaries and/or uterus at least 6 mo prior to dosing, or Essure® with hysterosalpingogram [documentation to confirm tubal occlusion 12 wk after procedure]).
   b. Naturally postmenopausal (spontaneous cessation of menses) for at least 12 consecutive mo prior to dosing, confirmed by follicle stimulating hormone (FSH) testing or estradiol testing.
3. Female subjects who are of childbearing potential must agree to nonhormonal methods of contraceptive therapy or refrain from sexual intercourse to prevent pregnancy until 1 mo postdose. If the subject is on oral contraceptive, the subject also needs to use a nonhormonal method in addition to oral contraceptive. Female subjects must refrain from breastfeeding for at least 2 weeks post dose.
4. Male subjects must agree to use a condom and spermicide during sexual intercourse until 1mo post dose or must have had a vasectomy and must be willing not to donate sperm until 1 mo post dose.
5. All subjects must agree not to donate blood, plasma, platelets, or any other blood components from Screening to 4 wk post dose.
6. All subjects must be willing to refrain from consuming grapefruit/grapefruit juice, Seville oranges, and pomegranates/pomegranate juice 10 d before the dose of study drug is given on Day 1 until End-of-Study (EoS).
7. All subjects must provide written informed consent prior to participating in the study.
8. Subjects with HI are required to have:
   a. Documented history of chronic liver disease diagnosed by ultrasonography, computed tomography scan, liver biopsy, or magnetic resonance imaging or history of chronic (>6 mo) hepatitis B virus (HBV) or hepatitis C virus (HCV) infection
   b. Moderate HI as assessed by NCI-ODWG criteria [total bilirubin (TBIL) >1.5 to 3x ULN (not due to Gilbert's syndrome)] and confirmed at Check in.
   c. Normal or clinically nonrelevant findings at physical examination and normal limits or clinically nonrelevant deviations in clinical laboratory evaluations, with exception of findings that in the opinion of investigator are consistent with subject's HI.
9. Creatinine Clearance ≥ 70 mL/min estimated using the Cockcroft Gault formula without any markers of chronic kidney disease at Screening and Check-in.
10. Clinical stability in the opinion of the investigator

4.2. Exclusion Criteria

Subjects who meet any of the following criteria will be disqualified from entering the study:

1. Clinically relevant abnormal history, physical findings, ECG, or laboratory values at the Screening assessment that could interfere with the objectives of the study or the safety of the subject
2. Subjects with primary biliary cirrhosis or primary sclerosing cholangitis
3. Concomitant medication (moderate or strong inhibitor or inducer of CYP3A4 [eg, itraconazole, rifampin], CYP2C9 [eg, fluconazole, carbamazepine] and UGT [eg, probenecid, rifampin]) within 2 wk before dosing and throughout study
4. History of stomach or intestinal surgery or resection that would potentially alter absorption and/or excretion of orally administered drugs (with the exception of appendectomy, hernia repair, and/or cholecystectomy)
5. Presence or history of severe adverse reaction to any drug (except penicillin)
6. A positive drugs of abuse screen (unless the drug is medically prescribed by a licensed health care provider) or alcohol breath test at Screening or at Check-in on Day -2 or a subject who will not agree to smoke ≤10 cigarettes or equivalent per day from Screening up to Enrollment, and is unable to be restricted to ≤5 cigarettes per day and for 6 h post dose during their period of residence in the clinical unit
7. Concomitant use of medications known to affect the elimination of serum creatinine (eg, trimethoprim or cimetidine) and inhibitors of renal tubular secretion (eg, probenecid) within 60 d of Day -2
8. History or presence of an abnormal ECG, which, in the investigator's opinion, is clinically significant and/or a QT interval corrected for heart rate using Fridericia's formula (QTcF) ≥450 milliseconds (ms) and ≥470 ms for healthy male and female subjects, respectively, and >500 ms for subjects with HI at Screening
9. Consumption of alcohol-within 72 h prior to Check-in and caffeine-containing beverages within 48 h prior to Check-in and during confinement
10. Consumption of more than 28 units of alcohol per wk for males or 14 units of alcohol per wk for females, where 1 unit of alcohol equals one-half pint of beer, 4 ounces (oz) of wine, or 1 oz of spirits, or significant history of alcoholism or drug/chemical abuse within the last 2 y
11. Positive serology for HBsAg and anti-HCV (healthy subjects), HAV immunoglobulin M, or anti-HIV Type 1 and Type 2 (all subjects)
12. Loss of more than 450 mL blood during the 3 mo before the trial (eg, as a blood donor)
13. Current enrollment in or have not yet completed at least 30 d or 5 elimination half-lives, whichever is longer, since receiving an investigational device or product, or receipt of other investigational agents within 30 d of pexidartinib
14. History of any malignancy (except basal cell carcinoma) in the past 5 y

15. In the opinion of the investigator, history of a clinically significant illness within 4 wk prior to administration of study drug
16. Participation in a previous pexidartinib study
17. Employment by the clinic or the Sponsor
18. Any other reason, in the opinion of the investigator, which precludes subject participation in the study
19. Familial relationship with another study participant

Additional Exclusion Criteria for Matched Healthy Subjects:

1. Any clinically relevant abnormality identified on the physical examination, ECG, vital signs, or laboratory tests at Screening.
2. Any clinically unstable, uncontrolled medical condition.
3. Liver function (AST, ALT, alkaline phosphatase of liver origin, and TBIL) test results above the upper limit of normal at Screening and on Day -2.
4. Use of any prescription or over-the-counter (OTC) medications (systemic or topical), vitamins, or dietary/herbal supplements within 14 d prior to study drug dosing, with the exception of acetaminophen (≤2 g/d), stool softeners, and topical hydrocortisone cream, which are permitted.

Additional Exclusion Criteria for Subjects with Hepatic Impairment:

1. Any clinically unstable, uncontrolled medical conditions other than those associated with HI.
2. Evidence of infection with HBV and/or new or acute HCV infection within the preceding 6 mo.
3. HI subjects maintained on a gastric pH modifier (eg, proton pump inhibitor), must be discontinued from this medication 7 d prior to and 24 h after pexidartinib administration. The subject should be switched to Gelusil (aluminum hydroxide, magnesium hydroxide, and simethicone) as needed for up to 48 h prior to the administration of pexidartinib. Gelusil use is prohibited from 48 h prior to the administration of pexidartinib to 24 h post pexidartinib dosing. At 24 h post pexidartinib, treatment with the usual gastric pH modifier can be resumed.
4. HI subjects maintained on oral or transdermal hormone replacement therapy for postmenopausal symptoms in females or hypogonadism in men are excluded from participating unless they have been discontinued for at least 28 d prior to pexidartinib administration and for 7 d post pexidartinib. Other hormonal replacement therapy for maintenance of chronic conditions (eg, insulin, thyroxin) is permitted. Oral contraceptives are permitted in women of childbearing potential.
5. Subjects with active Stage 3 or Stage 4 encephalopathy
6. Fluctuating or rapidly deteriorating hepatic function as indicated by recent history or worsening of clinical and/or laboratory signs of HI as judged by the investigator.

5. STUDY TREATMENTS

5.1. Assigning Subjects to Treatment Groups/Sequences and Blinding

5.1.1. Treatment Groups/Sequences

This is an open-label, 1-treatment, 1-period study.

Pexidartinib (1 × 200-mg capsule) will be administered orally to all subjects on the morning of Day 1 with 240 mL of water. Subjects will fast for at least 10 h before pexidartinib dosing and will continue to fast for at least 4 h after pexidartinib administration. Water ingestion is restricted from 1 h prior to and up to 2 h post pexidartinib administration.

Details for each study visit are provided in the study procedures (see Section 6) and in the Schedule of Events (see Section 16.5).

5.1.2. Method of Treatment Allocation

Subjects with HI will be recruited first. When all moderate HI subjects have received study drug, the group of healthy subjects with normal hepatic function can be enrolled. There is no randomization in this study.

5.1.3. Blinding

This is an open-label study. No blinding will be required.

5.1.4. Emergency Unblinding Procedure

Not applicable

5.2. Study Drug

5.2.1. Description

Pexidartinib is formulated as opaque, white, 200-mg capsules, which will be supplied by the Sponsor.

5.2.2. Labeling and Packaging

Adequate amounts of study drug will be provided in bottles, with contents identified on the label. Investigational product labels will include all of the information required by federal and local regulations. Applicable supporting product information on pexidartinib will be provided by the Sponsor.

5.2.3. Preparation

The study drug will be supplied as capsules that need no preparation at the study site.

5.2.4. Administration

Pexidartinib will be administered orally as a single dose of 1 × 200-mg capsule at the clinic with 240 mL of water following at least a 10-h overnight fast.

The study drug will be administered in accordance with the protocol. The study drug will be administered only to subjects participating in the clinical study. It is a violation of the regulations to use unapproved investigational medicinal products (IMPs) for purposes other than those stated in the protocol. The site will complete the required documentation as provided by Daiichi Sankyo, Inc. (DSI), or its representatives, to document dispensing of IMPs. All information will be recorded immediately on a drug-dispensing form each time the IMPs are dispensed to a subject.

5.2.5. Storage

Drug supplies must be stored in a secure, limited access storage area within the recommended storage conditions. DSI should be contacted if storage conditions fall outside the specified range. All drug supplies should be quarantined pending a decision from DSI.

5.2.6. Drug Accountability

When a drug shipment is received, the investigator or designee will check the amount, condition, and temperature recording of the study drug; check for appropriate local language on the label and drug expiration date; and sign the receipt of shipment form provided. The receipt of the shipment form should be faxed as instructed on the form. The original will be retained at the site. In addition, the investigator or designee shall contact the Sponsor as soon as possible if there is a problem with the shipment.

A drug accountability record will be provided for the IMPs or the site can use their own DSI-approved drug accountability log. The record must be kept current and should contain the dates and quantities of the drug received, the subject's identification number and/or initials or supply number, as applicable, to whom the IMP was dispensed, the date and quantity of the IMP dispensed and remaining (if from individual subject drug units), as well as the initials of the dispenser. The dispenser's information must be noted on the delegation of duties log.

At the end of the study, or as directed, all pexidartinib products, including unused, partially used, or empty containers, will be destroyed after full accountability per drug unit. If the pexidartinib products are destroyed at the study center, approval in writing from the Sponsor must be received, and the Sponsor must receive copies of the study center's drug handling and disposition standard operating procedures. Dosage form (ie, capsule) site-level accountability documentation is required as part of the disposition records of the IMP. The dosage form site-level accountability documentation should be appended to the Certificate of Destruction and provided to DSI.

The IMP will be returned to a designee, as instructed by the Sponsor, only if the study center is unable to perform the destruction of the products. The IMP will be returned only after the study monitor has completed a final inventory to verify the quantity to be returned. The return/destruction of IMPs must be documented, and the documentation must be included in the shipment. At the end of the study, a final IMP reconciliation statement must be completed by the investigator, or designee, and provided to the Sponsor.

Dosage form (ie, capsule) site-level accountability documentation must be included with each drug supply return shipment or other returning facility, such as another depot.

The aforementioned documentation is required as part of the receiving records for return shipments.

All IMP inventory forms must be made available for inspection by a Sponsor-authorized representative or designee and regulatory agency inspectors. The investigator is responsible for the accountability of all used and unused study drug at the site.

5.2.7. Retention Samples

Not applicable

5.3. Control Treatment

Not applicable

5.4. Dose Interruptions and Reductions

Not applicable

5.5. Method of Assessing Treatment Compliance

To ensure treatment compliance, all doses will be administered under the supervision of clinical study personnel. A mouth and hand check must be carried out in all the subjects to ensure that all the capsules have been swallowed.

The exact times of IMP dosing and the number of units administered will be recorded in the electronic Case Report Form (eCRF).

5.6. Prior and Concomitant Medications

Medications used within 30 d prior to Screening will be recorded.

All prescription or OTC medications (systemic and topical), vitamins, gastric pH modifiers, and dietary or herbal supplements will be prohibited 14 d before the dose of pexidartinib and for the duration of the study. St John's Wort (hypericin) should not have been taken within 30 d prior to the dose of pexidartinib (see Section 4.2). For HI subjects, concomitant medications required for a medical condition can be continued as long as they are not prohibited as noted below and by the specific exclusions in Section 4.2.

HI subjects maintained on a gastric pH modifier (eg, proton pump inhibitor), must be discontinued from this medication 7 d prior to and 24 h after pexidartinib administration. The subject should be switched to Gelusil (aluminum hydroxide, magnesium hydroxide, and simethicone) as needed for up to 48 h prior to the administration of pexidartinib. Gelusil use is prohibited from 48 h prior to the administration of pexidartinib to 24 h post pexidartinib dosing. At 24 h post pexidartinib, treatment with the usual gastric pH modifier can be resumed.

HI subjects maintained on oral or transdermal hormone replacement therapy for postmenopausal symptoms in females or hypogonadism in men are excluded from participating unless they have been discontinued for at least 28 d prior to pexidartinib administration and for 7 d post pexidartinib. Other hormonal replacement therapy for maintenance of chronic conditions (eg,

insulin, thyroxin) is permitted. Oral contraceptives are permitted in women of childbearing potential.

Acetaminophen (≤2 g/d) and topical hydrocortisone for contact dermatitis are allowed during the inpatient stay at the discretion of the investigator.

Any medication (other than study drug) taken by subjects during the course of the study will be recorded and coded using the World Health Organization (WHO) drug dictionary. If drug therapy other than that specified by the protocol is taken, a joint decision will be made by the investigator and the Sponsor whether to continue or discontinue that subject. On the day pexidartinib is taken, any concomitant oral medication that is required for a medical condition (eg, diabetes or hypertension) is to be taken at 8 h post dose.

5.6.1. Dietary and Lifestyle Restrictions

Subjects will fast (no food or drink other than water) overnight (at least 10 h) before the clinical laboratory safety tests on Day -2, at 48 h and 120 h post dose, and at Check-out / Early Termination (ET). After pexidartinib administration, subjects will continue to fast for 4 h post dose. Subjects will not be allowed water during the 1-h period before and 2-h period after each dose of pexidartinib.

A standard menu and meal schedule based on the United States (US) Recommended Daily Allowance will be employed uniformly to all subjects. Meals and/or snacks will be served at appropriate times thereafter. The calorie content, as well as the percent of calories from protein, carbohydrate, and fat, will be uniform for each meal during the study (eg, breakfast uniform to breakfast, lunch uniform to lunch).

Except when ECGs are performed, subjects will remain seated with minimal ambulation (ie, only to and from the washroom or for study procedures) for the first 4 h following pexidartinib administration.

Subjects must refrain from consuming grapefruit/grapefruit juice and Seville oranges for 7 d before administration of study drug on Day 1 until the EoS, and food or beverages containing caffeine/xanthine for 48 h prior to Check-in on Day -2 until the EoS or alcohol for 72 h prior to Check-in on Day -2 until the EoS. Subjects must not engage in vigorous exercise while residing in the Clinical Unit or within 7 d of entering the Clinical Unit.

Male subjects must use a condom and spermicide, and their female partners must use an additional method of nonhormonal contraception (such as a cap or diaphragm, or intrauterine device, if they are on an oral contraceptive, they need to use a nonhormonal method in addition to an oral contraceptive) for 1 mo post-dose, unless the subject's partner is postmenopausal or has had a hysterectomy, a bilateral salpingectomy, or a bilateral oophorectomy. Subjects must use a condom and spermicide if their partner has had a tubal ligation. For the 1-mo period post dose, male subjects must not have sex with a woman who is pregnant or breastfeeding, without using a condom. To protect partners from possible exposure to study drug in semen, male subjects must use a condom for the 1-mo period post dose, even if they have had a vasectomy or their partner is not of childbearing potential. Partners who are not of childbearing potential are defined as: men; postmenopausal women (no menstrual periods for at least 12 consecutive mo); or women who have undergone a hysterectomy, a bilateral oophorectomy, or a bilateral salpingectomy.

Subjects must not sunbathe or use a sunbed during the study.

5.7. Subject Withdrawal/Discontinuation

5.7.1. Reasons for Withdrawal

Any subject who discontinues from the study for any reason will have the date of discontinuation and reason(s) recorded. A subject will be considered a completer if he/she provides the last scheduled PK sample.

Subjects may be withdrawn from the study after signing informed consent for the following reasons:

- AE
- Withdrawal of consent by subject
- Physician decision
- Pregnancy
- Protocol deviation
- Study terminated by Sponsor
- Other

5.7.2. Withdrawal Procedures

If a subject is withdrawn from the study, the investigator will complete and report the observations as thoroughly as possible up to the date of withdrawal, including the date of last treatment and the reason for withdrawal.

If the subject is withdrawn due to an AE, the investigator will follow the subject until the AE has resolved or stabilized.

All subjects who are withdrawn from the study should complete protocol-specified withdrawal procedures.

5.7.3. Subject Replacement

Subjects with HI may be replaced with approval from the Sponsor.

5.7.4. Subject Re-testing Procedures

Potential HI subjects who have a disqualifying laboratory result will be allowed to re-test and, only upon qualifying for the study, will receive a subject number.

5.8. Criteria for Suspending Study Treatment

The subject will be discontinued from the study for reasons such as:

1. If any clinical laboratory abnormality is detected and considered clinically significant, at the discretion of the investigator and following discussion with the Sponsor.
2. If a subject presents any significant treatment emergent AE, as determined by the investigator.
3. If a subject uses concurrent medications specified in the exclusion criteria (Section 4.2).

6. STUDY PROCEDURES

This is a Phase 1, open-label, 1-treatment, 1-period study. A study visit schedule in tabular format is provided in Appendix 16.5.

6.1. Screening

Subjects will be screened Day -22 through Day -2.

The following activities and/or assessments will be performed:

Day -22 to Day -2 (Screening)

- Informed consent.
- Medical/surgical history, demographics, and inclusion/exclusion criteria.
- Complete physical examination.
- Urine drugs of abuse screen (opiates, benzodiazepines, amphetamines, cannabinoids, cocaine, barbiturates, phencyclidine), cotinine, and breath alcohol testing.
- Blood test for HIV antibody, HBsAg, and HCV or HAV antibody.
- Serum pregnancy test for female subjects.
- Serum FSH test for postmenopausal female subjects.
- Clinical laboratory tests for serum chemistry, hematology, coagulation (including PT and International Normalized Ratio [INR]), and urinalysis following at least a 10-h overnight fast. Subjects should not have ingested alcohol for 72 h prior to the visit.
- Single 12-lead ECGs after 10 min of rest in the supine position.
- Vital signs (diastolic blood pressure [DBP], systolic blood pressure [SBP], oral temperature, pulse, and respiratory rate) measured after at least 10 min of rest in the supine position; body weight, height, and BMI will be recorded.
- Record eGFR
- Record Child-Pugh score for subjects with moderate HI. This will be collected for information purpose only and will be included in the clinical database.
- Record hepatic impairment status by NCI-ODWG criteria for subjects with moderate HI. This will be used for inclusion/exclusion criteria and will be included in the clinical database.
- Record prior/concomitant medications.
- Record AEs and relatedness to treatments (drug and nondrug) given for AEs.

6.2. Subject Management

Not applicable

6.3. Randomization

Not applicable

6.4. Treatment Period

6.4.1. Check-in

Eligible subjects will be admitted to the clinic during Check-in on Day -2. Subjects will remain in the clinic until the completion of all study procedures, approximately 168 h (7 days) after oral administration of pexidartinib (see schedule of assessments). The following activities and/or assessments will be performed:

Day -2 (Check-in)

- Admission
- Medical/surgical history and inclusion/exclusion criteria.
- Complete physical examination.
- Urine drugs of abuse screen (opiates, benzodiazepines, amphetamines, cannabinoids, cocaine, barbiturates, phencyclidine), cotinine, and breath alcohol testing.
- Serum pregnancy test for female subjects.
- Clinical laboratory tests for serum chemistry, hematology, coagulation (including PT and INR), and urinalysis following at least a 10-h overnight fast. In the HI group, clinical lab tests for TBIL must be confirmed.
- Single 12-lead ECGs recorded after 10 min of rest in the supine position.
- Vital signs (DBP, SBP, oral temperature, pulse, and respiratory rate) measured after at least 10 min of rest in the supine position. Body weight will be recorded.
- Record eGFR
- Record prior/concomitant medications.
- Record AEs and treatments (drug and nondrug) given for AEs.
- Begin clinic confinement.

Day -1

- Record prior/concomitant medications.
- Record AEs and treatments (drug and non-drug) given for AEs.
- If deemed necessary by the PI, TBIL level may be reconfirmed in subjects with moderate HI.
- Record Child-Pugh classification score for information only.
- Clinic confinement.

6.4.2. Treatment Phase

The following activities and/or assessments will be performed:

6.4.2.1. Day 1 Dosing

- Single 12-lead ECGs will be recorded at predose (at 60 min prior to pexidartinib dosing) and at 1, 2, 3, and 4 h post-pexidartinib dose.
- Vital signs (DBP, SBP, oral temperature, pulse, and respiratory rate) will be measured at predose (at 60 min prior to pexidartinib dosing) and at 1, 2, 3, and 4 h post-pexidartinib dose.
- Pexidartinib dosing: subjects will receive 200 mg (1 × 200-mg capsule) of pexidartinib orally with 240 mL of water following at least a 10-h overnight fast; subjects will continue to fast for an additional 4 h after dosing.
- Blood samples (1 × 4-mL tube containing Li Heparin) will be collected for PK analysis of pexidartinib and ZAAD-1006a at predose (within 30 min prior to dosing) and at 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 8, 10, and 12 h post dose.
- A 10-mL blood sample will be obtained at 2.5 h post dose for plasma protein binding.
- Record prior/concomitant medications before and after pexidartinib dosing.
- Record AEs and relatedness to treatments (drug and non-drug) given for AEs before and after pexidartinib dosing.
- Clinic confinement.

6.4.2.2. Day 2 through Day 4

- Clinical laboratory tests for serum chemistry, hematology, coagulation (including PT and INR), and urinalysis following at least a 10-h overnight fast at 48 h post dose.
- Blood samples (1 × 4-mL tube containing Li Heparin) will be collected for PK analysis of pexidartinib and ZAAD-1006a at 24, 36, 48, and 72 h post dose.
- A 10-mL blood sample will be obtained at 24 h post dose for plasma protein binding.
- Record concomitant medications.
- Record AEs and relatedness to treatments (drug and non-drug) given for AEs.
- Clinic confinement.

6.4.2.3. Day 5 through Day 7

- Clinical laboratory tests for serum chemistry, hematology, coagulation (including PT and INR), and urinalysis following at least a 10-h overnight fast at 120 h post dose.
- Blood samples (1 × 4-mL tube containing Li Heparin) will be collected for PK analysis of pexidartinib and ZAAD-1006a at 96, 120, and 144 h post dose.
- Record concomitant medications.

- Record AEs and relatedness to treatments (drug and non-drug) given for AEs.
- Clinic confinement.

6.5. Washout

Not applicable

6.6. Check-out or Early Termination

Subjects will be discharged on Day 8 after they undergo the assessments described below. Subjects who withdraw from the study early will undergo the same assessments as those administered on Day 8:

- Complete physical examination.
- Urine pregnancy test for female subjects.
- Clinical laboratory tests for serum chemistry, hematology, coagulation (including PT and INR), and urinalysis following at least a 10-h overnight fast.
- Single 12-lead ECG will be recorded before breakfast and after 10 min of rest in the supine position.
- Vital signs (DBP, SBP, oral temperature, pulse, and respiratory rate) will be measured before breakfast and after at least 10 min in the supine position. Body weight will be recorded.
- Blood sample (1 × 4-mL tube containing Li Heparin) for PK analysis of pexidartinib and ZAAD-1006a at 168 h post dose.
- Record concomitant medications.
- Record AEs and relatedness to treatments (drug and non-drug) given for AEs.

6.7. Follow-up

Follow up will occur for any TEAE until resolved or stabilized.

7. PHARMACOKINETIC/PHARMACODYNAMIC ASSESSMENTS

7.1. Pharmacokinetic Assessments

Blood samples (1 × 4-mL tube containing Li Heparin) will be collected for PK analysis of pexidartinib and ZAAD-1006a metabolite, at predose (within 60 min prior to dosing) and at 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 8, 10, 12, 24, 36, 48, 72, 96, 120, 144, and 168 h post dose. Additional 10-mL samples will be collected to determine protein binding of pexidartinib and ZAAD-1006a at 2.5 and 24 h post dose.

Plasma will be harvested and analyzed for the quantification of pexidartinib using a validated liquid chromatography-tandem mass spectrometry method. The ZAAD-1006a metabolite will be analyzed using a qualified liquid chromatography-tandem mass spectrometry assay. Additional exploratory metabolite analysis may be conducted using the leftover plasma samples.

For the windows for PK blood sample collection and protein binding sample collection will follow the Daiichi Sankyo's Noncompartmental Analysis Guidelines.

PK blood sample collection should have priority over other study assessments. For other study assessments, in case the distribution of meals or time for study assessments coincide with the sample collection time, the sequence of events should be as follows: ECG, measurement of vital signs, blood sampling, and distribution of meals, unless stated differently. Deviations from the listed PK windows are regarded as protocol deviations. All other assessments should be completed within 30 min of the scheduled time point, the window for predose assessments can occur up to 90 min prior to dosing. Deviations from the scheduled time of all other procedures outside of 30 min will be regarded as protocol deviations.

The following PK parameters will be calculated by compartment-model-independent analysis, based on the total and unbound concentrations of pexidartinib in the plasma; Cmax, Tmax, AUClast, AUCinf, kel, t1/2, CL/F, and Vz/F. The following PK parameters will be calculated for ZAAD-1006a based on the total and unbound concentrations of ZAAD-1006a in the plasma: Cmax, Tmax, AUClast, AUCinf, and t1/2. The MPR will be determined based on total concentrations of pexidartinib and ZAAD-1006a.

PK analysis will be conducted in compliance with Daiichi Sankyo's Noncompartmental Analysis Guidelines.[6]

7.2. Pharmacodynamic Assessments

Not applicable

7.3. Immunogenicity

Not applicable

8. SAFETY EVALUATION AND REPORTING

8.1. Assessment of Safety Endpoint Events

The safety endpoints include physical examination findings, vital sign measurements, incidence of AEs, clinical laboratory test results (including AST/ALT), and ECG recordings.

8.2. Adverse Event Collection and Reporting

All clinical AEs (see Section 8.4.1 for definitions) occurring after the subject signs the ICF and up to 30 d after the final dose of pexidartinib, whether observed by the investigator or reported by the subject, will be recorded on the AE eCRF page. Medical conditions (including clinical laboratory values/vital signs that are out of range) that were diagnosed or known to exist prior to informed consent will be recorded as part of medical history.

All AEs, including serious adverse events (SAEs), are to be reported according to the procedures in Section 8.5.

All clinical laboratory results, vital signs, and ECG results or findings should be appraised by the investigator to determine their clinical significance. Isolated abnormal clinical laboratory test results, vital sign findings, or ECG findings (ie, not part of a reported diagnosis) should be reported as AEs if they are symptomatic, lead to study drug discontinuation, dose reduction, require corrective treatment, or constitute an AE in the investigator's clinical judgment.

At each time point, the investigator will determine whether any AEs have occurred by evaluating the subject. AEs may be directly observed, reported spontaneously by the subject or by questioning the subject at each time point. Subjects should be questioned in a general way, without asking about the occurrence of any specific symptoms. The investigator must assess all AEs to determine seriousness, severity, and causality, in accordance with the definitions in Section 8.4. The investigator's assessment must be clearly documented in the study site's source documentation with the investigator's signature.

Always report the diagnosis as the AE or SAE term. When a diagnosis is unavailable, report the primary sign or symptom as the AE or SAE term with additional details included in the narrative until the diagnosis becomes available. If the signs and symptoms are distinct and do not suggest a common diagnosis, report them as individual entries of AE or SAE.

For events that are serious due to hospitalization, the reason for hospitalization must be reported as the SAE (diagnosis or symptom requiring hospitalization). A procedure is not an AE or SAE, but the reason for the procedure may be an AE or SAE. Pre-planned (prior to signing the ICF) procedures or treatments requiring hospitalization for pre-existing conditions that do not worsen in severity should not be reported as SAEs (see Section 8.4.2 for definitions).

For deaths, the underlying or immediate cause of death should always be reported as an SAE.

Any serious, untoward event that may occur subsequent to the reporting period that the investigator assesses as related to study drug should also be reported and managed as an SAE.

The investigator should follow subjects with AEs until the event has resolved or the condition has stabilized. In case of unresolved AEs, including significant abnormal clinical laboratory

values at the end of study assessment, these events will be followed until resolution or until they become clinically not relevant.

8.3. Adverse Events of Special Interest

Adverse Events of Special Interest

Combined elevations of aminotransferases and bilirubin, either serious or nonserious and whether or not causally related, meeting the criteria of a potential Hy's Law case (total bilirubin level ≥2 × ULN with simultaneously ALT or AST ≥3 × ULN) should always be reported to the Sponsor as soon as possible following the procedures outlined in Section 8.5 for SAE reporting, with the investigator's assessment of seriousness, causality, and a detailed narrative.

8.4. Adverse Event

8.4.1. Definition of Adverse Event

An AE is any untoward medical occurrence in a subject administered a pharmaceutical product and that does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal clinical laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product (ICH E2A Guideline. Clinical Safety Data Management: Definitions and Standards for Expedited Reporting, October1994).

It is the responsibility of investigators, based on their knowledge and experience, to determine those circumstances or abnormal clinical laboratory findings which should be considered AEs.

8.4.2. Serious Adverse Event

An SAE is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect or
- Is an important medical event

Note: The term "life-threatening" in the definition of "serious" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe (ICH E2A Guideline. Clinical Safety Data Management: Definitions and Standards for Expedited Reporting, October 1994).

Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above. Examples

include allergic bronchospasm, convulsions, and blood dyscrasias or development of drug dependency or drug abuse.

Note:

Procedures are not AEs or SAEs, but the reason for the procedure may be an AE or SAE.

Pre-planned (prior to signing the ICF) procedures or treatments requiring hospitalizations for pre-existing conditions that do not worsen in severity are not SAEs.

8.4.3. Severity Assessment

The following definitions should be used to assess intensity of AEs (based on the National Cancer Institute Common Terminology Criteria for Adverse Events [CTCAE], version 5.0):

- Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
- Grade 2: Moderate; minimal, local, or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (eg, preparing for meals, shopping for groceries or clothes, using the telephone, managing money)
- Grade 3: Severe or medically significant, but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living (ie, bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden)
- Grade 4: Life-threatening consequences; urgent intervention indicated
- Grade 5: Death related to AE

8.4.4. Causality Assessment

The investigator should assess causal relationship between an AE and the study drug on the basis of his/her clinical judgment and the following definitions. The causality assessment must be made based on the available information and can be updated as new information becomes available.

- **Related:**
  - The AE follows a reasonable temporal sequence from study drug administration, and cannot be reasonably explained by the subject's clinical state or other factors (eg, disease under study, concurrent diseases, and concomitant medications).

  OR

  - The AE follows a reasonable temporal sequence from study drug administration, and it is a known reaction to the drug under study or its chemical group, or it is predicted by known pharmacology.
- **Unrelated:**

- The AE does not follow a reasonable sequence from study drug administration, or can be reasonably explained by the subject's clinical state or other factors (eg, disease under study, concurrent diseases, concomitant medications).

8.4.5. Action Taken for Event

- None
  - No treatment was required.
- Medication required.
  - Prescription and/or OTC medication was required to treat the AE.
- Other.

8.4.6. Adverse Event Outcome

- Recovered/Resolved
  - The subject fully recovered from the AE with no residual effect observed.
- Recovering/Resolving
  - The AE improved but has not fully resolved.
- Not recovered / Not resolved
  - The AE itself is still present and observable.
- Recovered / Resolved with Sequelae
  - The residual effects of the AE are still present and observable.
  - Include sequelae/residual effects.
- Fatal
  - Fatal should be used when death is a direct outcome of the AE.
- Unknown

8.5. Serious Adverse Events Reporting – Procedure For Investigators

All AEs, AESIs and SAEs will be reported in the eCRF.

The following types of events should be reported by the investigator on a SAVER (Serious Adverse Event Report) form within 24 h of awareness:

- SAEs and SAVERs (see Section 8.4.2 for definition)
- SAEs and AESIs should be reported by the investigator on a Serious Adverse Event Report (SAVER) form within 24 h of awareness (see Section 8.4.2 for the definition of an SAE).

All events (serious and non-serious) must be reported with the investigator's assessment of the event's seriousness, severity, and causality to the study drug. A detailed narrative summarizing

the course of the event, including its evaluation, treatment, and outcome should be provided. Specific or estimated dates of event onset, treatment, and resolution should be included when available. Medical history, concomitant medications, and clinical laboratory data that are relevant to the event should also be summarized in the narrative. For fatal events, the narrative should state whether an autopsy was or will be performed, and include the results if available. Source documents (including medical reports) will be retained at the site and should not be submitted to the Sponsor for SAE reporting purposes.

Urgent safety queries must be followed up and addressed promptly. Follow-up information and response to non-urgent safety queries should be combined for reporting to provide the most complete data possible within each follow-up.

All completed SAVER forms must be signed by the investigator and e-mailed to DSI at the following e-mail address: PPD. See Section 14.10.5 for contact information for SAE reporting. Please call the Sponsor's medical monitor for any questions on SAE reporting (Section 14.10.4).

Place the initial version of SAVER in the subject's file.

8.6. Notifying Regulatory Authorities, Investigators, and Institutional Review Board

DSI and/or Worldwide Clinical Trials Early Phase Services, LLC will inform investigators, Institutional Review Board (IRB) and regulatory authorities of all SAEs reported from this study, and any Suspected Unexpected Serious Adverse Reaction (SUSAR) occurring in other studies of the investigational drug, as appropriate per local reporting requirements. DSI and/or Worldwide Clinical Trials Early Phase Services, LLC will comply with any additional local safety reporting requirements.

In the US, upon receipt of the Sponsor's notification of SUSARs that occurred with the study drug, unless delegated to the Sponsor, it is the investigator's responsibility to inform the IRB per Sponsor's instruction.

8.7. Exposure in Utero During Clinical Studies

DSI must be notified of any subject who becomes pregnant while receiving or within 90 d of discontinuing the study drug.

DSI must be notified of any male subject whose female partner becomes pregnant while the subject is receiving or within 90 d of discontinuing the study drug. Reporting after ET is done voluntarily by the investigator.

Although pregnancy is not technically an AE, all pregnancies must be followed to conclusion to determine their outcome. This information is important both for drug safety and public health concerns. It is the responsibility of the investigator, or designee, to report any pregnancy in a female subject, or a male subject's female partner, using the exposure in utero (EIU) reporting form. Please contact your study monitor to receive the EIU reporting form upon learning of a pregnancy. The investigator should make every effort to follow the subject until completion of the pregnancy and complete the EIU Reporting form with complete pregnancy outcome information, including normal delivery and induced abortion. The adverse pregnancy outcome,

either serious or non-serious, should be reported in accordance with study procedures. If the outcome of the pregnancy meets the criteria for immediate classification as an SAE (ie, post-partum complications, spontaneous or induced abortion, stillbirth, neonatal death, or congenital anomaly, including that in an aborted fetus), the investigator should follow the procedures for reporting SAEs outlined in Section 8.5.

For reports of pregnancy in the female partner of a male subject, the EIU form (or SAE form if associated with an adverse outcome) should be completed with the subject's randomization number, initials, and date of birth, and details regarding the female partner should be entered in the narrative section.

8.8. Clinical Laboratory Evaluations

Blood samples for the following serum chemistry, hematology, and coagulation panels will be performed after at least a 10-h overnight fast at the time points indicated in Appendix 16.5. For clinical laboratory parameters, the reference range at the institution that performs the measurements will be used.

The serum chemistry profiles must be obtained under fasting conditions (approximately 10 h). Results of all laboratory tests will be included in the subject's eCRF.

The following clinical laboratory parameters will be evaluated:

- Serum chemistry (approximately 8.5 mL): sodium, potassium, magnesium, bicarbonate, chloride, calcium, inorganic phosphorus, AST, ALT, GGT, alkaline phosphatase, direct bilirubin, total bilirubin, glucose, creatinine, blood urea nitrogen, total protein, albumin, uric acid, creatine kinase, total cholesterol, and triglycerides.
- Hematology (approximately 4 mL): hemoglobin, hematocrit, red blood cell (RBC) count (with indices), reticulocyte count, white blood cell (WBC) count (with differential), and platelet count.
- Urinalysis: standard urinalysis, including a microscopic examination and specific gravity, pH, protein, glucose, ketones, blood, RBC, WBC, bilirubin, and urobilinogen.

Calculation of eGFR (using the Cockcroft-Gault equation) will be performed at Screening.

Tests for virology (HIV antibody, HBsAg, and HCV antibody) will be performed at Screening only.

Coagulation tests (PT/INR and aPTT).

Child-Pugh Score will be calculated at screening only for the subjects with moderate hepatic impairment for information purpose only.

8.9. Vital Signs

SBP, DBP, and pulse will be measured after the subject has rested in a supine position for 10 min or more.

Resting vital signs (blood pressure, heart rate, oral temperature, and respiratory rate) will be performed at Screening, predose and at 2, 24, and 144 h post dose, or Early Termination.

When vital signs measurements and a blood draw are scheduled for the same time point, the vital signs should be taken within approximately 5 min prior to the blood draw. Predose vital signs measurements will be taken at 1 h prior to the dose.

Body weight and height will be recorded at Screening. Body weight will also be recorded at Check-in and at Check-out, or Early Termination. BMI will be calculated at Screening.

Information will be entered in the eCRF on whether or not measured, date of measurement, and measurement results for the following items: SBP, DBP, pulse, respiratory rate, oral temperature, height, body weight, and BMI.

8.10. Electrocardiograms

The ECGs will be read on site as part of the safety assessments. Whether measurement is performed, date performed, results, and findings will be recorded in the eCRF.

The single 12-lead ECGs should be performed after at least 10 min of quiet rest in the supine position (see time points indicated in Appendix 16.5). Before electrodes are removed, the electrode position is to be marked on the skin with indelible ink and the same electrode position used for all subsequent ECGs during confinement for each subject. When a blood draw is scheduled concomitantly with an ECG, the ECG should be taken within 10 min prior to the blood draw. Predose ECGs will be taken at 1 h prior to the dose.

8.11. Physical Examinations

A complete physical examination will be performed by a medically qualified person at the time points indicated in Appendix 16.5. A medically qualified person will perform the physical exam. The physical examination will include an evaluation of the respiratory, cardiovascular, gastrointestinal, dermatological, musculoskeletal, psychiatric, and neurologic systems, as well as the head, eyes, ears, nose, and throat.

8.12. Drug and Alcohol Screen

A urine screen for alcohol, cotinine, and drugs of abuse will be performed for all subjects at Screening and at Check-in. Alcohol, cotinine, amphetamines, barbiturates, benzodiazepines, cocaine, opiates, phencyclidine and cannabinoids will be included in the assay.

8.13. Pregnancy Test

For all female subjects, serum pregnancy tests will be performed at Screening, Check-in and Check-out or Early Termination. Dosing on Day 1 will be contingent upon a negative result.

8.14. Serum FSH

At Screening, should a female subject report postmenopausal status not induced by surgical sterilization, a serum FSH measurement will be obtained.

8.15. Other Examinations

A urine screen for cotinine and drugs of abuse (amphetamines, barbiturates, benzodiazepines, cocaine, opiates, phencyclidine, and cannabinoids) will be performed for all subjects at the time

points indicated in Appendix 16.5. Breath alcohol testing will also be performed at the time points indicated in Appendix 16.5. For female subjects of childbearing potential, a qualitative serum or urine pregnancy test will be performed at the time points indicated in Appendix 16.5. For all postmenopausal female subjects, an FSH test will be performed at Screening.

9. OTHER ASSESSMENTS

Not applicable

10. STATISTICAL METHODS

10.1. General Statistical Considerations

All PK and safety data obtained in this study will be displayed in data listings and, if appropriate, summarized using descriptive statistics. A detailed Statistical Analysis Plan (SAP) describing the methodology to be used in the final analysis will be prepared and finalized prior to the database lock. Changes to the statistical analyses will require a protocol amendment only if principal features of the protocol are changed. Any deviations from the planned statistical analyses in the protocol will be fully described in the SAP and the clinical study report.

Categorical data will be presented in contingency tables with cell frequencies and percentages for the subject population.

In general, data will be summarized for the moderate hepatic impairment group and the subjects with normal hepatic function. For point estimations of key PK parameters, 90% confidence intervals (CIs) for HI/normal hepatic function will be calculated (see Section 10.4.1).

For the data analysis, missing data will not be imputed; analyses will be performed on observed data only, unless otherwise noted.

Raw data will be presented with the exact precision with which they were collected.

10.2. Analysis Sets

10.2.1. Pharmacokinetic Analysis Set

The PK Analysis Set will include all subjects who received a dose of pexidartinib and have sufficient plasma concentration data to characterize the PK parameters. The impact of clinically relevant events that may affect the estimate of PK parameters will be assessed while analyzing data and handled appropriately. Any exclusion will be clearly delineated in the report.

Individual plasma concentrations of pexidartinib and ZAAD-1006a will be reported for all subjects.

10.2.2. Safety Analysis Set

The Safety Analysis Set will include all subjects who received a dose of pexidartinib.

10.3. Study Population Data

The safety subject population will be summarized for demographic characteristics. Continuous demographic variables (age [calculated from the date of birth to the date when the ICF was signed], body weight, height, and BMI) for all subjects will be summarized with descriptive statistics for both groups. Categorical demographic variables (sex, race, and ethnicity) will be summarized with frequency counts and corresponding percentages.

Medical history data, physical examination data, and prior/concomitant medications will be listed.

10.4. Statistical Analysis

10.4.1. Pharmacokinetic Analyses

The PK Analysis Set will be used for all PK analyses. Descriptive statistics will be presented for pexidartinib and ZAAD-1006a plasma concentrations at each evaluation time point and for all quantitative PK parameters of pexidartinib and ZAAD-1006a.

Plasma concentration-time data will be analyzed using noncompartmental methods. The following PK parameters of pexidartinib will be calculated using both total and unbound plasma concentrations: Cmax, Tmax, AUClast, AUCinf, kel, t1/2, CL/F, and Vz/F. Plasma PK parameters (Cmax, Tmax, AUClast, AUCinf, t1/2) will be calculated based on both total and unbound plasma concentrations of ZAAD-1006a.

PK parameters for pexidartinib and ZAAD-1006a will be assessed by descriptive statistics for the HI group and matching control group. The metabolite-to-parent ratio for AUClast and AUCinf for total concentrations, adjusted for molecular weight, will be determined for the HI and normal hepatic function groups.

Cmax, AUClast, and AUCinf of pexidartinib (based on total and unbound plasma concentrations) will be compared for the HI group and those of normal hepatic function. These comparisons between the HI group with the matched control group will be made using an analysis of variance model. The resulting point estimates (geometric least squares means), their ratios (HI/normal hepatic function), and 90% confidence intervals (CIs) for the ratios will be presented.

10.4.2. Pharmacodynamic Analyses

Not applicable

10.4.3. Pharmacogenomic Analyses

Not applicable

10.4.4. Safety Analyses

All safety analyses will be performed using the Safety Analysis Set. The number and percentage of subjects reporting TEAEs will be tabulated by the Medical Dictionary for Regulatory Activities (MedDRA) system organ class (SOC) and preferred term with a breakdown by degree of HI (ie, moderate HI and normal hepatic function) and overall. ECG interval measurements and other safety endpoints will be summarized using descriptive statistics by degree of HI when appropriate.

10.4.4.1. Adverse Event Analyses

AEs will be coded by the MedDRA. All AEs, including SAEs, will be mapped to SOC and preferred term and will be listed in the data listing.

A TEAE is defined as an AE that emerges during treatment, having been absent pre-treatment, or worsens relative to the pre-treatment state. The number and percentage of subjects reporting

TEAEs will be calculated overall, by SOC, by preferred term, and by hepatic function group. TEAEs will be further summarized by CTCAE grade and relationship to study drug.

Any AE that starts prior to dosing with any study drug is considered a pretreatment AE.

Any AE that starts after a specified monitoring period is considered a post-treatment AE.

A by-subject AE (including treatment-emergent) data listing including but not limited to verbatim term, preferred term, SOC, CTCAE grade, and relationship to study treatment will be provided. Deaths, other SAEs, and other significant AEs will be listed.

10.4.4.2. Clinical Laboratory Evaluation Analyses

Descriptive statistics will be provided for the clinical laboratory results by scheduled time of evaluation and by hepatic function group for the Safety Analysis Set, as well as for the change from baseline. The baseline value is defined as the last non-missing value before the initial administration of study treatment. In addition, mean changes from baseline will be presented by for subjects with moderate HI and healthy subjects with normal hepatic function for the maximum and minimum post-treatment values and the values at Check-out.

Abnormal clinical laboratory results will be graded according to National Cancer Institute CTCAE version 5.0, if applicable, and the grade will be presented in a by-subject data listing. A shift table, presenting the 2-way frequency tabulation for baseline and the worst post-treatment value according to the CTCAE grade, by hepatic function group, will be provided for clinical laboratory tests. Abnormal clinical laboratory results deemed of clinical significance or of Grade 3 or 4 will be listed.

10.4.4.3. Vital Sign Analyses

Vital signs measurements will be listed by scheduled time of evaluation and by hepatic function group for the Safety Analysis Set, as well as for the change from baseline. The baseline value is defined as the last non-missing value before the administration of study drug.

10.4.4.4. Electrocardiogram Analyses

Descriptive statistics will be provided for the ECG measurements (PR, RR, QRS, and QT intervals, and QT interval corrected for heart rate using Bazett's formula (QTcB) and QTcF intervals where the QT intervals corrected for heart rate by the Bazett's and Fridericia's formulas [$QTcB = QT/(RR)^{1/2}$ and $QTcF = QT/(RR)^{1/3}$ respectively]) by scheduled time of evaluation and by hepatic function group for the Safety Analysis Set, as well as for the change from baseline.

The last non-missing value before pexidartinib administration will serve as baseline.

The number and percentage of subjects with absolute QT, QTcF, and QTcB intervals in the pre-specified categories (>450, >480, and >500 ms), and the change from baseline in QT, QTcF, and QTcB intervals (>30 and >60ms) will be summarized by hepatic function group and overall.

10.4.4.5. Physical Examination Analyses

Results of physical examinations will be displayed in a listing.

10.4.4.6. Exploratory Safety Analyses

Not applicable

10.4.4.7. Other Safety Analyses

Not applicable

10.5. Sample Size Determination

Sixteen subjects will be enrolled. Half of these subjects will be moderate HI and the other half will be healthy subjects with normal hepatic function matched by age, gender, and body weight. The sample sizes are not based on statistical considerations. The number of subjects is considered sufficient to achieve the study objectives (see FDA Guidance 2003).[7] Subjects who discontinue after receiving study drug will not be replaced unless approved by the sponsor.

10.6. Statistical Analysis Process

To preserve the integrity of the statistical analyses and clinical study conclusions, the SAP will be finalized prior to database lock.

All statistical analyses will be performed using SAS® Version 10.6 or higher (SAS Institute, Cary, NC 27513).

11. DATA INTEGRITY AND QUALITY ASSURANCE

The investigational site will permit study-related monitoring, audits, IRB review, and regulatory inspections by providing direct access to source data/documents. Direct access includes permission to examine, analyze, verify, and reproduce any records and reports that are important to the evaluation of a clinical study.

11.1. Monitoring and Inspections

The DSI/CRO monitor and regulatory authority inspectors are responsible for contacting and visiting the investigator for the purpose of inspecting the facilities and, upon request, inspecting the various records of the study (eg, eCRFs, source data, and other pertinent documents).

The verification of adherence to the protocol; completeness, accuracy, and consistency of the data; and adherence to ICH Good Clinical Practice (GCP) and local regulations on the conduct of clinical research will be accomplished through a combination of onsite visits by the monitor and review of study data remotely. The frequency of the monitoring visit will vary based on the activity at each site. The monitor is responsible for inspecting the eCRFs and ensuring completeness of the study essential documents. The monitor should have access to subject medical records and other study-related records needed to verify the entries on the eCRFs. Detailed information is provided in the monitoring plan.

The monitor will communicate deviations from the protocol, Standard Operating Procedures, GCP, and applicable regulations to the investigator and will ensure that appropriate action(s) designed to prevent recurrence of the detected deviations is taken and documented.

The investigator agrees to cooperate with the monitor to ensure that any problems detected in the course of these monitoring visits are addressed to the satisfaction of the Sponsor and documented.

In accordance with ICH GCP and the Sponsor's audit plans, this study site may be selected for audit by representatives from the Sponsor. Audit of site facilities (eg, pharmacy, drug storage areas, laboratories) and review of study related records will occur in order to evaluate the study conduct and compliance with the protocol, ICH GCP, and applicable regulatory requirements. The investigator should respond to audit findings. In the event that a regulatory authority informs the investigator that it intends to conduct an inspection, the Sponsor shall be notified immediately.

11.2. Data Collection

DSI or a designee will supply eCRFs. An eCRF must be completed for each subject who signs an ICF and receives a dose of pexidartinib. All data collected during the study will be recorded in this individual, subject-specific eCRF. Instructions will be provided for the completion of the eCRF and any corrections made will be automatically documented via the electronic data capture (EDC) software's "audit trail."

Completion of the eCRF should be kept current to enable the monitor to review the subject's status throughout the course of the study. All information and other material to be used by subjects and investigative staff must use vocabulary and language that are clearly understood. The eCRF will be completed, reviewed, and signed off or e-signed by the investigator. The

investigator will sign and date the indicated places on the eCRF via the EDC system's electronic signature. These signatures will indicate that the investigator inspected or reviewed the data on the eCRF, the data queries, and the study site notifications, and agrees with the content. Screen failure information will be collected at the site and will not be reported in the EDC.

11.3. Data Management

Each subject will be identified in the database by a unique subject identifier as defined by the Sponsor.

To ensure the quality of clinical data across all subjects and study sites, a Clinical Data Management review will be performed on subject data according to specifications given to DSI. Data will be vetted both electronically and manually for eCRFs and the data will be electronically vetted by programmed data rules within the application. Queries generated by rules and raised by reviewers will be generated within the EDC application. During this review, subject data will be checked for consistency, completeness, and any apparent discrepancies.

Data received from external sources such as central laboratories will be reconciled to the clinical database.

SAEs in the clinical database will be reconciled with the safety database.

All AEs will be coded using MedDRA. Prior and concomitant medication entered into the database will be coded using the WHO drug dictionary (Version 18.1 or higher).

11.4. Study Documentation and Storage

The investigator will maintain a Signature List of appropriately qualified persons to whom he/she has delegated study duties. All persons authorized to make entries and/or corrections on eCRFs will be included on the Signature List.

Investigators will maintain a confidential screening log of all potential study candidates that includes limited information of the subjects, dates, and outcomes of screening process.

Investigators will be expected to maintain an Enrollment Log of all subjects enrolled in the study indicating their assigned study number.

Investigators will maintain a confidential subject identification code list. This confidential list of names of all subjects allocated to study numbers on enrolling in the study allows the investigator to reveal the identity of any subject when necessary.

Source documents are original documents, data, and records from which the subject's eCRF data are obtained. These include but are not limited to hospital records, clinical and office charts, laboratory and pharmacy records, diaries, microfiches, X-rays, and correspondence.

Records of subjects, source documents, monitoring visit logs, data correction forms, eCRFs, inventory of study drug, regulatory documents (eg, protocol and amendments, IRB correspondence and approvals, approved and signed ICFs, investigator's agreement, clinical supplies receipts, distribution and return records), and other Sponsor correspondence pertaining to the study must be kept in appropriate study files at the study site (Trial Master File). Source documents include all recordings and observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical study. These

records will be retained in a secure file for the period required by the institution or study site policy. Prior to transfer or destruction of these records, the Sponsor must be notified in writing and be given the opportunity to further store such records.

11.5. Record Keeping

The investigator and study staff are responsible for maintaining a comprehensive and centralized filing system (Trial Master File) of all study-related documentation, suitable for inspection at any time by representatives from the Sponsor and/or applicable regulatory authorities. The Trial Master File includes:

- Subject files containing completed eCRFs, ICFs, and supporting copies of source documentation (if kept).
- Study files containing the protocol with all amendments, IB, copies of relevant essential documents required prior to commencing a clinical study, and all correspondence to and from the IRB and the Sponsor.
- Records related to the study drug including acknowledgment of receipt at site, accountability records, final reconciliation, and applicable correspondence.

In addition, all original source documents supporting entries in the eCRFs must be maintained and be readily available.

The Trial Master File will be retained by the investigator until at least 3 y after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 3 y have lapsed since the formal discontinuation of clinical development of the investigational drug. These documents should be retained for a longer period, however, if required by the applicable regulatory requirements or by an agreement with the Sponsor. It is the responsibility of the Sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

The subject's medical files should be retained in accordance with applicable legislation and in accordance with the maximum period of time permitted by the hospital, institution, or private practice.

No study document should be destroyed without prior written agreement between the Sponsor and the investigator. Should the investigator wish to assign the study records to another party or move them to another location, he/she must notify the Sponsor in writing of the new responsible person and/or the new location.

12. FINANCING AND INSURANCE

12.1. Finances

Prior to starting the study, the investigator and/or institution will sign a clinical study agreement with DSI. This agreement will include the financial information agreed upon by the parties.

12.2. Reimbursement, Indemnity, and Insurance

The Sponsor provides insurance for study subjects to make available compensation in case of study-related injury.

Reimbursement, indemnity, and insurance shall be addressed in a separate agreement on terms agreed upon by the parties.

13. PUBLICATION POLICY

A study site may not publish results of a study until after a coordinated multicenter publication has been submitted for publication or until 1 y after the study has ended, whichever occurs first. Therefore, the study site will have the opportunity to publish the results of the study, provided that DSI has had the opportunity to review and comment on the study site's proposed publication prior to its being submitted for publication with the prior advice of DSI Legal Affairs (intellectual property council) and with proper regard to the protection of subjects' identities.

14. ETHICS AND STUDY ADMINISTRATIVE INFORMATION

14.1. Compliance Statement, Ethics and Regulatory Compliance

This study will be conducted in compliance with the protocol, the ethical principles that have their origin in the Declaration of Helsinki, the ICH consolidated Guideline E6 for GCP (Committee for Medicinal Products for Human Use/ICH/135/95), and applicable regulatory requirements including the following:

- European Commission Directive (2001/20/EC April 2001)
- European Commission Directive (2005/28/EC April 2005)
- US FDA GCP Regulations: Code of Federal Regulations Title 21, parts 11, 50, 54, 56, and 312 as appropriate
- Japanese Ministry of Health, Labor and Welfare Ordinance No. 28 of 27 March 1997
- The Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics No. 1 of 25 November 2014 and/or
- Other applicable local regulations

14.2. Subject Confidentiality

The investigators and the Sponsor will preserve the confidentiality of all subjects taking part in the study, in accordance with GCP and local regulations.

The investigator must ensure that the subject's anonymity is maintained. On the eCRFs or other documents submitted to the Sponsor or the CRO, subjects should be identified by a unique subject identifier as designated by the Sponsor. Documents that are not for submission to the Sponsor or the CRO (eg, signed ICF) should be kept in strict confidence by the investigator.

In compliance with ICH GCP Guidelines, it is required that the investigator and institution permit authorized representatives of the company, of the regulatory agency(ies), and the IRB direct access to review the subject's original medical records for verification of study-related procedures and data. The investigator is obligated to inform the subject that his/her study-related records will be reviewed by the above-named representatives without violating the confidentiality of the subject.

14.3. Informed Consent

Before a subject's participation in the study, it is the investigator's responsibility to obtain freely given consent, in writing, from the subject after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study and before any protocol-specific procedures or any study drug is administered. Subjects should be given the opportunity to ask questions and receive satisfactory answers to their inquiries and should have adequate time to decide whether or not to participate in the study. The written ICF should be prepared in the local language(s) of the potential subject population.

In obtaining and documenting informed consent, the investigator should comply with the applicable regulatory requirements, and should adhere to GCP and to the ethical principles that have their origin in the Declaration of Helsinki. The consent form and any revision(s) should be approved by the IRB prior to being provided to potential subjects.

The subject's written informed consent should be documented in the subject's medical records. The ICF should be signed and personally dated by the subject and by the person who conducted the informed consent discussion (not necessarily the investigator). The original signed ICF should be retained in accordance with institutional policy, and a copy of the signed consent form should be provided to the subject. The date and time (if applicable) that informed consent was given should be recorded on the eCRF.

If the subject cannot read, then according to ICH GCP Guideline Section 4.8.9, an impartial witness should be present during the entire informed consent discussion. This witness should sign the ICF after the subject has consented to the subject's participation and, if possible, signed the ICF. By signing the ICF, the witness attests that the information in the ICF and any other written information was adequately explained to and apparently understood by the subject and that informed consent was freely given by the subject.

Suggested model text for the ICF for the study and any applicable subparts (PK, etc) are provided in the Sponsor's ICF template for the investigator to prepare the documents to be used at his or her study site. Updates to applicable forms will be communicated via letter from the Sponsor.

Additional consent is required for Health Insurance Portability and Accountability Act. Subjects will consent to virology testing (HIV antibody, HBsAg and HCV antibody) as part of their initial informed consent. This testing will be described in the ICF.

14.4. Regulatory Compliance

The study protocol, subject information and consent form, the IB, any subject written instructions to be given to the subject, available safety information, subject recruitment procedures (eg, advertisements), information about payments and compensation available to the subjects, and documentation evidencing the investigator's qualifications should be submitted to the IRB for ethical review and approval according to local regulations, prior to the study initiation. The written approval should identify all documents reviewed by name and version.

Changes in the conduct of the study or planned analysis will be documented in a protocol amendment and/or the SAP.

The investigator and/or Sponsor must submit and, where necessary, obtain approval from the IRB for all subsequent protocol amendments and changes to the ICF. The investigator should notify the IRB of deviations from the protocol or SAEs occurring at the study site and other AE reports received from the Sponsor/CRO, in accordance with local procedures.

As required by local regulations, the Sponsor's local Regulatory Affairs group or representative to whom this responsibility has been delegated will ensure all legal aspects are covered, and approval from the appropriate regulatory bodies obtained, prior to study initiation. If changes to the initial protocol and other relevant study documents are made, this representative will also ensure that any revised documents required for submission are submitted to regulatory

authorities and implementation of these changes happen only after approval by the relevant regulatory bodies, as required.

In the event of any prohibition or restriction imposed (eg, clinical hold) by an applicable Regulatory Authority in any area of the world, or if the investigator is aware of any new information which might influence the evaluation of the benefits and risks of the investigational drug, the Sponsor should be informed immediately.

In addition, the investigator will inform the Sponsor immediately of any urgent safety measures taken by the investigator to protect the study subjects against any immediate hazard, and of any suspected/actual serious GCP non-compliance that the investigator becomes aware of.

14.5. Protocol Deviations

The investigator should conduct the study in compliance with the protocol agreed to by the Sponsor and, if required, by the regulatory authority, and which was given approval/favorable opinion by the IRB.

A deviation to any protocol procedure or waiver to any stated criteria will not be allowed in this study except where necessary to eliminate immediate hazard(s) to the subject. The Sponsor must be notified of all intended or unintended deviations to the protocol (eg, inclusion/exclusion criteria, dosing, missed study visits) on an expedited basis.

The investigator, or person designated by the investigator, should document and explain any deviation from the approved protocol.

If a subject was ineligible or received the incorrect dose or study treatment, and had at least 1 administration of study drug, data should be collected for safety purposes.

If applicable, the investigator should notify the IRB of deviations from the protocol in accordance with local procedures.

14.6. Supply of New Information Affecting the Conduct of the Study

When new information becomes available that may adversely affect the safety of subjects or the conduct of the study, the Sponsor will inform all investigators involved in the clinical study, IRB, and regulatory authorities of such information, and when needed, will amend the protocol and/or subject information.

The investigator should immediately inform the subject whenever new information becomes available that may be relevant to the subject's consent or may influence the subject's willingness to continue participation in the study. The communication should be documented on medical records, for example, and it should be confirmed whether the subject is willing to remain in the study.

If the subject information is revised, it must be re-approved by the IRB. The investigator should obtain written informed consent to continue participation with the revised written information even if subjects were already informed of the relevant information. The investigator or other responsible personnel who provided explanations and the subject should sign and date the revised ICF.

14.7. Protocol Amendments

Any amendments to the study protocol that seem to be appropriate as the study progresses will be communicated to the investigator by the Sponsor. Also, the Sponsor will ensure the timely submission of amendments to regulatory authorities.

Changes made by protocol amendments will be documented in a Summary of Changes document. These protocol amendments will undergo the same review and approval process as the original protocol.

A protocol amendment may be implemented after it has been approved by the IRB and by regulatory authorities where appropriate, unless immediate implementation of the change is necessary for subject safety.

14.8. Study Termination

The Sponsor has the right to terminate the study at any time and study termination may also be requested by a competent authority.

14.9. Data and Safety Monitoring Board

Not applicable.

14.10. Address List

14.10.1. Sponsor's Clinical Study Leader

PPD
Consultant, Clinical Pharmacology
Quantitative Clinical Pharmacology
Daiichi Sankyo, Inc.
211 Mount Airy Road
Basking Ridge, NJ 07920
PPD

14.10.2. Sponsor's Clinical Study Manager

PPD
Associate Director
Clinical Operations Early Development
Daiichi Sankyo, Inc.
211 Mount Airy Road
Basking Ridge, NJ 07920
PPD

14.10.3. Sponsor's Pharmacokinetics Reviewer

PPD
Director, Clinical Pharmacology
Quantitative Clinical Pharmacology
Daiichi Sankyo, Inc.
211 Mount Airy Road
Basking Ridge, NJ 07920
PPD

14.10.4. Sponsor's Medical Monitor

PPD
Senior Director
Clinical Development, Oncology
Daiichi Sankyo, Inc.
211 Mount Airy Road
Basking Ridge, NJ 07920
PPD

14.10.5. Sponsor's Safety Contacts

Daiichi Sankyo Pharma Development
Clinical Safety and Pharmacovigilance
Email to: PPD

14.10.6. EDC Vendor

Worldwide Clinical Trials, Ltd
1st Floor, Waterfront House
Beeston Business Park
Beeston, Nottingham
NG9 1LA, UK
PPD

14.10.7. Bioanalytical Vendor

PPD
Bioanalytical Principal Investigator
Celerion
621 Rose Street
Lincoln, NE 68502
PPD

PPD
www.celerion.com

14.10.8. Central Laboratory

EccoLab Group
8370 W. Flagler St. Suite 216
Miami, FL 33144

14.10.9. Sponsor's Biostatistician

PPD
Biostatistics and Data Management
Daiichi Sankyo, Inc.
211 Mount Airy Road
Basking Ridge, NJ 07920
PPD

14.10.10. Data and Safety Monitoring Board

Not applicable

14.10.11. CRO

Worldwide Clinical Trials Early Phase Services, LLC
2455 N.E. Loop 410, Suite 150
San Antonio, TX 78217
PPD

14.10.11.1.CRO Investigator

PPD
Clinical Pharmacology of Miami (CPMI)
550 West 84th Street
Miami, Florida 33014-3616

PPD
Orlando Clinical Research Center (OCRC)
5055 South Orange Avenue
Orlando, Florida 32809

14.10.11.2.CRO Project Manager

PPD
Worldwide Clinical Trials
2455 N.E. Loop 410, Suite 150
San Antonio, TX 78217

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15. REFERENCES

1. PLX3397 Investigator's Brochure, Version 10.0 19 DEC 2018.
2. PLX108-11 CSR.
3. Turalio™ USPI (USPI-TUR-08919-r001)
4. Patel H, Egorin MJ, Remick SC, Mulkerin D, Takimoto CHM, Doroshow JH, et al. Comparison of Child-Pugh (CP) criteria and NCI organ dysfunction working group (NCI-ODWG) criteria for hepatic dysfunction (HD): Implications for chemotherapy dosing. J Clin Oncol. Jul.2004 22(14_suppl):6051.
5. PL3397-A-U114 CSR
6. Daiichi Sankyo Noncompartmental Analysis Guidelines 2019.
7. FDA Hepatic Guidance 2003.

16. APPENDICES

16.1. Labeling and Packaging

Not applicable

16.2. Blood Collection Volume by Category and Total

16.2.1. Blood Collection Volumes

Time Point	Test Item	Collection Volume (mL)	Frequency[a]	Total Volume (mL)[a]
Screening	Hematology test	4.0	1	25.2
	Blood coagulation system test	2.7		
	Blood chemistry test	8.5		
	Test for infections	10.0		
Check-in (Day -2)	Hematology test	4.0	1	15.2
	Blood coagulation system test	2.7		
	Blood chemistry test	8.5		
Treatment	Hematology test	4.0	3	45.6
	Blood coagulation system test	2.7		
	Blood chemistry test	8.5		
Treatment	Pexidartinib PK	4.0	23	92
	Protein binding	10.0	2	20
Check-out/ET	Hematology test	4.0	1	15.2
	Blood coagulation system test	2.7		
	Blood chemistry test	8.5		
		Total	31	213.2

[a] Blood collection in subjects with AEs should be continued until resolution of the events (even after the scheduled observation period). Blood to be used for several different tests but taken at 1 time will be counted as 1 collection (eg, FSH).
Note: For females, an additional 4 mL of blood may be taken for serum pregnancy testing at Screening and on Day -2.
Abbreviations: AE = adverse event; ET = Early Termination; FSH = follicle stimulating hormone; PK = pharmacokinetics

16.3. Additional Information (for Japanese Study Sites Only)

Not applicable.

16.3.1. GCP compliance

Not applicable.

16.3.2. Study Period

Not applicable.

16.3.3. Payment for Participation, Compensation for Study-Related Injuries, and Insurance

Not applicable.

16.3.4. Study Administrative Structure

Not applicable.

16.4. Instructions for Specimen Collection, Storage and Shipment

16.4.1. Plasma Pharmacokinetic Sample Collection, Storage and Shipment Instructions

A 2 mL blood sample will be taken by venipuncture of forearm vein(s) at time points detailed in the Schedules of Events (Section 16.5).

Blood samples will be collected into pre-chilled 2 mL Vacutainer® tubes containing lithium heparin as anticoagulant for the preparation of plasma. It is important to fill the Vacutainer® tubes to the specified collection volume.

The tube containing blood for plasma preparation will be gently inverted multiple (>8) times to ensure thorough mixing of anticoagulant and blood, then immediately placed in a cool box containing ice water. The samples should be centrifuged within 30 min after collection, at approximately 1500 g for approximately 10 min at approximately +4°C. Immediately following centrifugation, the separated plasma for each sample will be divided into 2 aliquots at the following volumes:

- Aliquot 1 (for pexidartinib assay): 0.5 mL
- Aliquot 2 (back-up for pexidartinib assay): remaining plasma

The 2 aliquots of plasma should each be pipetted into polypropylene cryogenic sample storage vials (at least 2 to 3 mL size, with screw-cap), designated Set 1 and Set 2, and labeled with appropriate information (barcode and/or subject ID, time points, and aliquot number). The aliquots must be kept chilled for the entire time before they are transferred to the freezer. Each set of aliquots must be stored in separate boxes. Within 60 min after blood draw, the sample storage vials will be stored in the dark in a -20°C (-15°C to -30°C) freezer.

Any sample anomalies should be recorded on the sampling forms.

Set 1 samples will be sent to the bioanalytical laboratory at Celerion for the determination of pexidartinib plasma concentrations. Set 1 samples should be shipped after the end of each period to arrive at the bioanalytical laboratory at Celerion the next day. Set 2 samples can be shipped to the bioanalytical laboratory at Celerion once the site confirms receipt of Set 1 samples from a period.

Shipping Guide

- Biological samples (eg, plasma) should be shipped on dry ice.

- Samples should be shipped only on a Monday, Tuesday, Wednesday, or Thursday to minimize the possibility of them being in transit over a weekend.
- If duplicate samples are being shipped, 1 set of samples should be sent. The second set should be shipped after receiving confirmation of arrival of the first set at Celerion.

Sample Packing

- Arrange the sample collection, with courier.
- Use a Styrofoam box, for example 19" × 19" × 12". Use a larger one if shipping many samples.
- Obtain 20 lbs of dry ice pellets. Use as much dry ice as possible, to help safeguard against any possible delays.
- Place a 4" layer of dry ice in the bottom of the Styrofoam box.
- Samples should be identified using self-adhesive labels, which should be applied prior to freezing the samples.
- Place the samples in boxes per standard site procedure. Place the boxes in the Styrofoam cooler and fill the excess space with the remaining dry ice pellets.
- Record the estimated weight of the dry ice used per box.
- Place the lid on the Styrofoam box and seal completely with tape.
- Tape a list of the samples contained inside the box, to the lid (eg, plasma, subjects 1 - 24, predose, 30 min, 1h). In order to protect this paperwork insert it into a plastic bag.
- Place the Styrofoam box in a cardboard shipping carton, seal securely with tape.

Labeling

Label the cardboard box as follows:

- Mark the outside of the cartons with tally number eg, 1 of 3, 2 of 3, and 3 of 3.
- Affix an address label, with the information below, to the outside of each box:

Celerion

Attn: Sample Receipt, Celerion
624 Peach Street Lincoln, NE 68502
PPD

Affix the following labels on each box:

- 1 carbon dioxide label with the weight included.

- 2 labels with internationally recognized dry ice symbols (Class 9) - 1 on either side of the box.

- 1 KEEP FROZEN label

- 1 PERISHABLE GOODS label
- Indicate return address and contact person on each carton.

Paperwork to Accompany Shipment

- These human biological samples are not known to be infectious or hazardous.
- For laboratory use only.
- $_____ for customs (a nominal value, eg, $5.00)
- No commercial value.

Beginning with the first shipment, include all of the following information:

- Subject identification
- Time point identification
- Protocol number
- Sponsor name

Any missing information may cause a delay in analysis.

Notify Celerion by email or fax immediately after the samples have been collected by the courier. Please provide the following information:

- Name of courier or transport company
- Date and time the shipment left your premises
- The airway bill number

The contact or sample receipt is:

Celerion
621 Rose Street
Lincoln, NE 68502

PPD

If the shipment labeling and documentation are not completed correctly, the shipment may be delayed.

Upon arrival at Celerion, the shipment will be unpacked, the contents will be documented, and the sender will be advised of its safe arrival.

16.5. Schedule of Events

16.5.1. Schedule of Events

Study Period →	Screening[a]	Check-in	Treatment															
Study Day→	-22 to -2	-2	-1	1														
				Hour Post Dose														
Study Event ↓ Study Hour →				Predose	0.5	1	1.5	2	2.5	3	3.5	4	4.5	5	6	8	10	12
Informed Consent	X																	
Admission		X																
Inclusion/Exclusion Criteria	X	X																
Demographic Information	X																	
Medical/Surgical History	X	X																
Complete Physical Examination	X	X																
Body Weight, height[b], and BMI[b]	X	X																
Urine Drugs of Abuse, Cotinine, Alcohol Screen[c]	X	X																
Virology (HBsAg/HIV/HAV/HCV)	X																	
Serum Pregnancy Test[d]	X	X																
FSH[e]	X																	
Hematology, Serum Chemistry, Urinalysis[f]	X	X																
Hepatic Function Status (NCI-ODWG criteria)	X	X	X															
Child-Pugh score (information only)	X		X															
Coagulation (PT, INR and aPTT)	X	X																

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Study Period →	Screening[a]	Check-in	Treatment														
Study Day→	-22 to -2	-2	-1	1													
				Hour Post Dose													
Study Event ↓ Study Hour →				Predose	0.5	1	1.5	2	2.5	3	3.5	4	4.5	5	6	8	10	12
12-lead ECGs[g]	X	X		X[h]		X		X		X		X						
Vital Signs (BP, pulse, respiratory rate, oral temperature)[i]	X	X		X		X		X		X		X						
Pexidartinib Administration[j]				X														
PK Blood Samples				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Protein Binding Samples									X									
Record eGFR	X	X																
AE Monitoring	X	X	←----------continuous ----------→															
Prior/Concomitant Medications	←----------continuous ----------→																	
Clinic Confinement		←----------continuous ----------→																

Abbreviations: AE = adverse event; BMI = body mass index; BP = blood pressure; d = day(s); ECG = electrocardiogram; eGFR = estimated glomerular filtration rate; ET = Early Termination; FSH = follicle stimulating hormone; HAV = hepatitis A virus; HCV = hepatitis C virus; HBsAg = hepatitis B surface antigen; HIV = human immunodeficiency virus; h = hour(s); INR = International Normalized Ratio; PK = pharmacokinetic; PT = prothrombin time

[a] To be conducted within 21 d prior to dosing.

[b] Height and BMI at Screening only.

[c] A breath test is also acceptable for alcohol screening.

[d] Female subjects only.

[e] Naturally postmenopausal female subjects only.

[f] Samples for serum chemistry will be collected after a 10-h fast.

[g] Single ECG after at least 10 min of quiet rest in the supine position. When a blood collection is scheduled concomitantly with an ECG, the ECG should be taken within 10 min prior to the blood collection.

[h] At 60 min prior to pexidartinib dosing.

[i] Vital signs will be taken after at least a 10-min supine rest.

[j] Pexidartinib will be administered following an overnight fast of 10 h. Water consumption will be restricted from 1 h predose to 2 h post dose, except for the specified amount that is to be administered with study drug. Subjects will continue to fast for 4 h post dose.

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Study Period →	**Treatment**							
Study Day→	**2 through 7**				**ET/Check-out[a]**			
	Hour Post Dose							
Study Event ↓ Study Hour →	**24**	**36**	**48**	**72**	**96**	**120**	**144**	**168**
Medical/Surgical History								
Complete Physical Examination								X
Body Weight and BMI[b]								X
Drug, Cotinine, Alcohol Screen								
Urine Pregnancy Test[c]								X
Hematology, Serum Chemistry, Urinalysis[d]			X			X		X
Coagulation (PT, INR, and aPTT)			X			X		X
12-lead ECGs[e]								X
Vital Signs (BP, pulse, respiratory rate, oral temperature)[f]								X
PK Blood Samples	X	X	X	X	X	X	X	X[g]
Protein Binding Sample	X							
AE Monitoring	←----------continuous----------→							
Concomitant Medications	←----------continuous----------→							
Clinic Confinement	←----------continuous----------→							

Abbreviations: AE = adverse event; BMI = body mass index; BP = blood pressure; d = day(s); ECG = electrocardiogram; eGFR = estimated glomerular filtration rate; ET = Early Termination; FSH = follicle stimulating hormone; HAV = hepatitis A virus; HCV = hepatitis C virus; HBsAg = hepatitis B surface antigen; HIV = human immunodeficiency virus; h = hour(s); INR = International Normalized Ratio; PK = pharmacokinetic; PT = prothrombin time

[a] Following final blood collections; same procedures to be performed at ET as at Check-out.

[b] BMI at Screening only.

[c] Female subjects only.

[d] Samples for serum chemistry will be collected after a 10-h fast.

[e] Single ECG after at least 10 min of quiet rest in the supine position. When a blood collection is scheduled concomitantly with an ECG, the ECG should be taken within 10 min prior to the blood collection.

[f] Vital signs will be taken after at least a 10-min supine rest.

[g] PK blood sample to be collected prior to Check-out procedures.

16.6. Inducers and Inhibitors of Drug Metabolizing Enzymes

Inhibitors

Inhibitors compete with other drugs for a particular enzyme thus affecting the optimal level of metabolism of the substrate drug which in many cases affect the individual's response to that particular medication, eg, making it ineffective.

■ **A Strong inhibitor** is one that causes a >5-fold increase in the plasma AUC values or more than 80% decrease in clearance.
■ **A Moderate inhibitor** is one that causes a >2-fold increase in the plasma AUC values or 50% to 80% decrease in clearance.
■ **A Weak inhibitor** is one that causes a >1.25-fold but <2-fold increase in the plasma AUC values or 20% to 50% decrease in clearance.

FDA preferred[1] and acceptable[2] **inhibitors** for in vitro experiments.*

1A2	2B6	2C8	2C9	2C19	2D6	2E1	3A4,5,7
■fluvoxamine	clopidogrel	■gemfibrozil[2]	■fluconazole[2]	PPIs:	■bupropion	diethyl-dithiocarbamate[2]	HIV Antivirals:
■ciprofloxacin	thiotepa			esomeprazole	■cinacalcet	disulfiram	■indinavir
	ticlopidine[2]	■trimethoprim[2]	■amiodarone	lansoprazole	■fluoxetine		■nelfinavir
■cimetidine	voriconazole			omeprazole2	■paroxetine		■ritonavir
		glitazones	efavirenz	pantoprazole	■quinidine1		
amiodarone		montelukast[1]	fenofibrate				■clarithromycin
efavirenz		quercetin[1]	fluconazole		■duloxetine		■itraconazole[1]
fluoroquinolones			fluvastatin	Other:	■sertraline		■ketoconazole
fluvoxamine			fluvoxamine[2]	chloramphenicol	■terbinafine		■nefazodone
furafylline[1]			isoniazid	cimetidine			■saquinavir
interferon			lovastatin	felbamate	■amiodarone		■ suboxone
methoxsalen			metronidazole	fluoxetine	■cimetidine		■telithromycin
mibefradil			paroxetine	fluvoxamine			
ticlopidine			phenylbutazone	indomethacin	celecoxib		■aprepitant
			probenicid	isoniazid	chlorpheniramine		■erythromycin
			sertraline	ketoconazole	chlorpromazine		■fluconazole
			sulfamethoxazole	modafinil	citalopram		■grapefruit juice
			sulfaphenazole[1]	oral	clemastine		■verapamil[2]
			teniposide	contraceptives	clomipramine		■diltiazem

voriconazole	oxcarbazepine	cocaine	
zafirlukast	probenicid	diphenhydramine	cimetidine
	ticlopidine2	doxepin	
	topiramate	doxorubicin	amiodarone
	voriconazole	escitalopram	azithromycin
		halofantrine	chloramphenicol
		haloperidol	boceprevir
		histamine H1	ciprofloxacin
		receptor antagonists	delaviridine
		hydroxyzine	diethyl-
		levomepromazine	dithiocarbamate
		methadone	fluvoxamine
		metoclopramide	gestodene
		mibefradil	imatinib
		midodrine	mibefradil
		moclobemide	mifepristone
		perphenazine	norfloxacin
		promethazine	norfluoxetine
		ranitidine	starfruit
		reduced-haloperidol	telaprevir
		ritonavir	voriconazole
		ticlopidine	
		tripelennamine	

Inducers

1A2	2B6	2C8	2C9	2C19	2D6	2E1	3A4,5,7
broccoli brussel sprouts carbamazepine char-grilled meat insulin methylcholanthrene[1] modafinil nafcillin beta-naphthoflavone[1] omeprazole[1] rifampin tobacco	artemisinin carbamazepine efavirenz nevirapine phenobarbital phenytoin rifampin	rifampin[1]	carbamazepine enzalutamide nevirapine phenobarbital rifampin secobarbital St. John's Wort	carbamazepine efavirenz enzalutamide norethindrone NOT pentobarbital prednisone rifampicin[1] ritonavir St. John's Wort	dexamethasone rifampin	ethanol isoniazid	