CLINICAL STUDY PROTOCOL

A PHASE 1, OPEN-LABEL, RANDOMIZED, 3-PERIOD CROSSOVER STUDY TO ASSESS THE EFFECT OF LOW-FAT FOOD ON PEXIDARTINIB PHARMACOKINETICS IN HEALTHY SUBJECTS

PL3397-A-U128

IND NUMBER 105,521

VERSION 1.0, 20 MAR 2019

DAIICHI SANKYO, INC.

211 MT. AIRY ROAD
BASKING RIDGE, NJ 07920

INVESTIGATOR AGREEMENT

A PHASE 1, OPEN-LABEL, RANDOMIZED, 3-PERIOD CROSSOVER STUDY TO ASSESS THE EFFECT OF LOW-FAT FOOD ON PEXIDARTINIB PHARMACOKINETICS IN HEALTHY SUBJECTS

Sponsor Approval:

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

[redacted]
Print Name

[redacted]
Signature

Clinical Study Leader

25 MAR 2019
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 consolidated guidelines on Good Clinical Practice (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 a 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.

[redacted]
Print Name

[redacted]
Signature

Principal Investigator
Title

28 /MAR/2019
Date (DD MMM YYYY)

PROTOCOL SYNOPSIS

EudraCT:	Not applicable
IND Number:	105,521
Protocol Number:	PL3397-A-U128
Investigational Product:	Pexidartinib hydrochloride (HCl) capsules 200 mg
Active Ingredient/INN:	Pexidartinib
Study Title:	A Phase 1, Open-Label, Randomized, 3-Period Crossover Study to Assess the Effect of Low-Fat Food on Pexidartinib Pharmacokinetics in Healthy Subjects
Study Phase:	Phase 1
Indication Under Investigation:	Not Applicable.
Study Objectives:	**Primary Objectives** The primary objectives of this study are: • To assess the effect of low-fat food on the pharmacokinetics (PK) of pexidartinib following a single oral dose of 400 mg administered in healthy subjects • To assess the PK of pexidartinib following a single oral dose of 200 mg administered with low-fat food in healthy subjects **Secondary Objective** The secondary objective of this study is: • To characterize the safety and tolerability of pexidartinib in healthy subjects following administration of a single oral dose of pexidartinib with low fat food and without food
Study Design:	This is an open-label, randomized, 3-treatment, 3-period crossover study in healthy subjects. In the first period, subjects will check in on Day -1 and receive treatment on Day 1, as per the randomization schedule. The subjects will continue to stay in the clinic and receive pexidartinib on Day 1 of each period as per the randomization schedule. Subjects will be randomized to 1 of 6 sequences: ABC, ACB, BAC, BCA, CAB, and CBA. Treatments are as follows: Treatment A: Single oral 400 mg (2 × 200 mg capsules) dose of pexidartinib in the morning under fasting conditions with 240 mL of water Treatment B: Single oral 400 mg (2 × 200 mg capsules) dose of pexidartinib in the morning within 30 minutes (min) after a low-fat standard breakfast meal Treatment C: Single oral 200 mg (1 × 200 mg capsule) dose of pexidartinib in the morning within 30 min after a low-fat standard breakfast meal

	Subjects in Treatment A will fast overnight for at least 10 hours (h) prior to dosing. Subjects in Treatments B and C will fast overnight for at least 10 h until 30 min prior to dosing, at which time they will be administered a low-fat standard breakfast which must be entirely consumed within 30 min. Subjects in all treatments will fast for at least 4 h following dosing. Water will be allowed ad libitum up to 1 h prior to dosing and starting at 2 h after dosing. There will be a washout of at least 6 days (d) between each dose of pexidartinib. Subjects will be confined at the clinic from Check-in to at least 144 h after the Period 3 dose. In each period, blood samples (1 × 2 mL) will be collected for PK analysis at predose (within 30 min prior to dosing) and 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 8, 10, 12, 14, 22, 24, 28, 32, 36, 48, 54, 60, 72, 84, 96, 108, 120, 132, and 144 h postdose. Plasma will be harvested and analyzed for pexidartinib using a validated liquid chromatography-tandem mass spectrometry (LC-MS/MS) method. 12-lead electrocardiograms (ECGs) will be performed at Screening, predose and at 2, 24 and 144 h postdose in each study period, at Check-out of Period 3 or Early Termination. Vital signs (blood pressure, heart rate, oral temperature, and respiratory rate) will be performed at Screening, predose and at 2, 24, and 144 h postdose in each study period, at Check-out of Period 3 or Early Termination. Clinical laboratory tests (hematology, serum chemistry, and urinalysis) will be performed at Screening, Check-in to Period 1, Day 7 of each period and at Check-out of Period 3 or Early Termination. A physical examination will be performed at Screening, Check-in to Period 1 and check-out of Period 3 or Early Termination. Adverse events and concomitant medication will be collected throughout the study.
Study Duration:	Subjects will be screened no more than 21 d prior to dosing on Day 1 of Period 1. The duration of the study (from Check-in to Check out) will be approximately 21 d.
Study Sites and Location:	The study will be conducted in 1 clinical site, at Worldwide Clinical Trials in San Antonio, Texas, USA
Subject Eligibility Criteria:	Subjects will be healthy males or non-childbearing potential females, 18 to 60 years (y) of age, inclusive and body mass index of 18 to 30 kg/m^2, inclusive.
Dosage Form, Dose and Route of Administration:	Treatment A: Single oral 400 mg (2 × 200 mg capsules) of pexidartinib in the morning under fasting conditions with 240 mL of water Treatment B: Single oral 400 mg (2 × 200 mg capsules) of pexidartinib with 240 mL of water in the morning within 30 min of a low-fat standard breakfast

	Treatment C: Single oral 200 mg (1 × 200 mg capsule) of pexidartinib with 240 mL of water in the morning within 30 min of a low-fat standard breakfast
Study Endpoints:	Pharmacokinetics: Plasma concentration time data for pexidartinib will be analyzed using noncompartmental methods. The following PK parameters will be reported: maximum observed concentration in plasma (Cmax), time to maximum observed concentration (Tmax), and area under the concentration-time curve from time of dosing to last measurable concentration (AUClast) and area under the concentration-time curve from time of dosing to infinity (AUCinf). Terminal half-life (t1/2), apparent total body clearance (CL/F), and apparent volume of distribution (Vz/F) will also be reported. Safety: Safety endpoints include ECG assessments (QT, PR, QRS, RR, and QTc [QTcB, QTcF] intervals), vital sign measurements, clinical laboratory tests, adverse events, and findings from physical examinations.
Planned Sample Size:	Twenty-four subjects will be randomized, with the expectation that at least 21 will complete all 3 periods of the study. The sample size is not determined based on statistical considerations, but to obtain adequate precision for the estimation. Discontinued subjects will not be replaced.
Statistical Analyses:	Pharmacokinetics: Individual and arithmetic mean (standard deviation [SD]) plasma concentration over time will be presented graphically for all treatments using linear and semilog scales. Descriptive statistics will be presented for each evaluation time point for plasma concentrations and for all quantitative PK parameters of pexidartinib. The peak (Cmax) and total exposures (AUClast, AUCinf) of pexidartinib will be compared between Treatments B and A using an appropriate analysis of variance (ANOVA) for the logarithm-transformed values of Cmax, AUClast, and AUCinf. Within the framework of the ANOVA, the 2-sided 90% confidence intervals (CIs) for ratios of treatment central values will be calculated by exponentiation of the corresponding 90% CIs for the treatment difference between the least squares means calculated for the logarithm-transformed values. Safety: Vital sign measurements and other safety endpoints will be summarized with descriptive statistics by treatment when appropriate. Tabulations will be provided for categorical data. ECGs will be read on site as part of the safety assessments. ECG endpoints will be summarized with descriptive statistics by treatment. Descriptive statistics will also be calculated at each time point for the changes from baseline by treatment.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

ABBREVIATION	DEFINITION
AE	adverse event
AESI	adverse event of special interest
ALP	serum alkaline phosphatase
ALT	serum alanine aminotransferase
AST	serum 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 time up to the time of the last quantifiable concentration
CCG	Case Report Form Completion Guideline
CDISC	Clinical Data Interchange Standards Consortium
CFR	Code of Federal Regulations
CL/F	apparent total body clearance
Cmax	maximum concentration
CRF	Case Report Form
CRO	Contract Research Organization
CSPV	Clinical Safety and Pharmacovigilance
CTCAE	Common Terminology Criteria for Adverse Events
d	day(s)
DMC	Data Monitoring Committee
EC	Ethics Committee
eCCG	Electronic Case Report Form Completion Guideline
ECG	electrocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
FAS	Full Analysis Set
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
h	hour(s)

ABBREVIATION	DEFINITION
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
INN	International Non-proprietary Name
IRB	Institutional Review Board
IRT	Interactive Response Technology
IXRS	Interactive Web/Voice Response System
MedDRA	Medical Dictionary for Regulatory Activities
min	minute(s)
mo	month(s)
ms	millisecond(s)
NCI	National Cancer Institute
OTC	over-the-counter
PD	pharmacodynamic
PGx	pharmacogenomics
PK	pharmacokinetic
PPS	per-protocol set
SAE	serious adverse event
SAP	Statistical Analysis Plan
SAVER	Serious Adverse Event Report
SUSAR	suspected unexpected serious adverse reaction
TBiL	total bilirubin
TEAE	treatment-emergent adverse event
T1/2	terminal elimination half-life
Tmax	time to reach maximum concentration
UGT	UDP-glucuronosyltransferase
Vz/F	apparent volume of distribution
wk	week(s)
y	year(s)

1. INTRODUCTION

1.1. Background

Pexidartinib is a novel, orally active, small molecule inhibitor that targets 3 kinases: CSF1R (also known as FMS), the receptor for CSF-1 (also known as M-CSF) as well as the ligand IL-34, KIT, the receptor for SCF, and oncogenic FLT3-ITD mutant, but remains highly selective versus other kinases. The potent inhibition of these three 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, 4) reprogramming tumor immune microenvironment, and 4) disrupting osteolytic metastases.[1]

The role of CSF-1 and its receptor Fms has been elucidated in the rare connective tissue neoplasia known as pigmented villonodular synovitis (PVNS).[2] This disease is generally characterized by hypersecretion of CSF-1 as a result of a translocation within synovial cells of the CSF-1 gene behind the collagen COL6A3 promoter. The resulting tumor occasionally involves expression of Fms on the tumor cells and leads to the recruitment of Fms-expressing monocytes and macrophages. Indeed, the pigment that characterizes the tumor mass is derived primarily from hemosiderin-laden macrophages. The strong genetic link between PVNS and CSF-1/Fms provides solid scientific rationale to treat PVNS patients with pexidartinib as a therapy targeting the underlying genetic defect.

A brief summary of data related to pexidartinib preclinical and clinical experience thus far is presented below and details can be found in the Investigator's Brochure.[1]

1.2. Data Summary

1.2.1. Nonclinical Studies

1.2.1.1. Safety Pharmacology

Two in vitro studies, conducted under qualified Good Laboratory Practice (GLP) conditions, examined the effects of pexidartinib on several electrophysiological parameters, with particular attention to potential for pexidartinib to prolong cardiac repolarization, which has been associated with the risk of torsades de pointes, a potentially lethal cardiac arrhythmia. When evaluated in human embryonic kidney (HEK) cells into which the gene coding for the human ether a go-go (hERG) channel, which is associated with an outward potassium current, an inhibitory concentration of 50% (IC50) of 0.7 μM was obtained. This IC50 value is considerably less potent than that for reference control agents, such as E-4031 or terfenadine, which typically have IC50 values in the nanomolar range. More importantly, in experiments to evaluate pexidartinib's potential effects on this cardiac repolarizing current, albumin or other proteins were absent in the assay buffer. Thus, all test article was free, unbound agent. Using equilibrium dialysis, pexidartinib was observed to bind plasma proteins extensively(> 99%). Thus, this should be taken into account in interpreting the results of these studies. The high

protein binding has the effect of raising the functional IC50 versus hERG channel inhibition for pexidartinib by a factor of 100, that is, 70 µM.

Additional follow-up studies evaluated the electrophysiological effects of pexidartinib on rabbit cardiac Purkinje fibers in vitro. In this assay, no meaningful test article-related effects on action potential duration, action potential amplitude or speed of cardiac depolarization (as judged by dV/dtmax) were observed. Because pexidartinib binds to the hERG channel yet no QT prolongation has been identified nonclinically, an investigative safety pharmacology study was conducted to examine potential binding to the L type calcium channel (hCav1.2) whose inhibition has been negatively correlated with risk for QT prolongation. IC50 for the inhibitory effect of pexidartinib on hCav1.2 calcium current was determined to be 0.2 µM.

In addition to the above in vitro studies, the hemodynamic and electrocardiographic effects of pexidartinib were evaluated in conscious, telemetry-equipped male Beagle dogs at doses of 50, 300, and 1000 mg/kg. Pexidartinib plasma exposures were 62969 ng·h/mL and 335633 ng·h/mL in animals given 50 and 1000 mg/kg pexidartinib, respectively. Importantly no QT interval corrected for heart rate (QTc) prolongation was seen. No test article-related effects were noted for the QTc interval up to the maximum dose tested (1000 mg/kg). All electrocardiographic parameters were qualitatively and quantitatively within normal limits. Left ventricular contractility (LV dP/dtmax) values were significantly lower by 833 and 815 mmHg/sec compared to vehicle controls in dogs that received 300 and 1000 mg/kg, respectively. Additionally, pexidartinib dose-dependently lowered the arterial pulse pressure. Based on these results, oral administration of pexidartinib could have pharmacodynamic effects on arterial pulse pressure and LV dP/dtmax that could translate into reduced contractility. Therefore, on the basis of this in vivo study, it is not anticipated that pexidartinib will produce QT prolongation, but pexidartinib does have the potential to affect hemodynamics and cardiac contractility.

The central nervous system (CNS) and respiratory safety pharmacology of pexidartinib were evaluated in female rats at doses of 20, 60, and 200 mg/kg. No test article-related adverse effects were observed in either of these studies. On the basis of those studies, a no-observed-effect-level (NOEL) was determined to be 200 mg/kg.

1.2.1.2. Nonclinical Pharmacokinetics and Drug Metabolism

Pexidartinib is orally bioavailable in all preclinical species (mouse, rat, dog and monkey). Pexidartinib is extensively bound to plasma protein irrespective of the species (mouse, rat, dog, human). After intravenous administration in nonclinical studies, the terminal elimination half-life (t1/2) values were 3.5 h in mice, 5.1 h in rats, 1.9 h in dogs, and 3.7 h in monkeys.

An in vitro study using recombinant human cytochrome P450 (CYP) indicated that CYP3A4 and CYP3A5 were the major isoforms responsible for pexidartinib metabolism. Additionally, CYP2D6, CYP2C8, CYP2C9, and CYP2C19 might play minor roles. Di-oxygenated, hydrogenated, and N-dealkylated pexidartinib were formed as the major CYP-mediated metabolites. The N-glucuronide of pexidartinib, ZAAD-1006a, was mainly produced by UGT1A4.

1.2.1.3. Toxicology

Nine in vivo toxicology studies were completed in rats and dogs, with 3 studies in each of these 2 species performed under GLP conditions.

The initial 2 GLP toxicology studies involved once daily (QD) in rats and twice daily in dogs via oral (gavage) administration of pexidartinib for 4 weeks (wk), with 16-day (d) (rat) or 14-d (dog) recoveries. Neither a NOEL nor a no-adverse-effect-level (NOAEL) of pexidartinib could be determined in either species in these studies due to toxicity seen at the lowest dose. The significant adverse, test article-related observations seen in these 2 high-dose GLP studies appear to be related to the mechanism of pexidartinib-mediated inhibition of Fms and Kit kinase. pexidartinib-related histopathologic observations included testicular spermatogonia reduction, bone marrow hypocellularity, thymic lymphoid reduction, bone hyperostosis and hypertrophy, ovarian follicular degeneration and liver hepatocellular hypertrophy. All adverse findings were partially or fully reversible. Two additional GLP toxicology studies at lower dose levels involved daily (QD in rats and dogs) oral (gavage) administration of pexidartinib for 4 weeks, with 8-wk recoveries at doses of 0.5, 2, and 10 mg/kg/d in rats, and 1, 6, and 30 mg/kg/d in dogs. NOAELs of pexidartinib were determined to be 10 mg/kg/d in rats and 6 mg/kg/d in dogs in these additional studies. All adverse findings were fully reversible, including testicular spermatogonia reduction. Two 13-wk GLP toxicology studies involved daily (QD in rats and dogs) oral (gavage) administration of pexidartinib for 13 weeks, with 8-wk recoveries at doses of 0.5, 4, and 20 mg/kg/d in rats, and 1, 6, and 30 mg/kg/d in dogs. NOAELs of pexidartinib were determined to be 4 mg/kg/d in rats and 6 mg/kg/d in dogs in these additional studies. No new target organ toxicities were defined in either study; reproductive toxicity findings (spermatogonial reduction) and increased incidence of emesis established in the dog at 30 mg/kg were demonstrated to be reversible. Anemia and bone marrow depletion, and hepatocellular vacuolation associated with increased liver enzymes were seen in the rat.

Potential effects of pexidartinib on embryofetal development in rats were assessed at 4, 10, and 40 mg/kg/d in a definitive study. Based on changes in hematology parameters at 40 mg/kg/d in the dams and fetal external and visceral malformations and skeletal developmental variations (findings primarily related to decreases in ossification) in the fetuses at 40 mg/kg/d, a dose level of 10 mg/kg/d was considered to be the NOAEL.

Pexidartinib showed no potential to cause phototoxicity in vitro in the NIH 3T3 fibroblast assay. In three genotoxicity studies, pexidartinib did exert any mutagenic or clastogenic effects.

1.2.1.4. Clinical Experience

A comprehensive series of nonclinical and clinical (N=14) studies and analyses elucidated the PK and PD and the influence of intrinsic and extrinsic factors on the PK of pexidartinib human exposure has been evaluated in 6 clinical studies.

Pexidartinib is an orally bioavailable drug with a terminal elimination half-life of 27 hours (h). Pexidartinib is metabolized mainly by UDP-glucuronosyltransferase (UGT)1A4 and cytochrome P450 (CYP)3A and undergoes minimal urinary elimination as unchanged drug. Strong inhibitors of these metabolic pathways increase pexidartinib exposures. CYP3A inducers, like rifampin deceases pexidartinib exposure. Concurrent administration of systemic pH modifiers (eg, esomeprazole) reduces pexidartinib exposure by approximately 40 to 50%. No dose adjustment

is needed for subjects with renal impairment including patients on routine hemodialysis. Administration of pexidartinib with food (high fat meal) increased exposure approximately 2-fold. Therefore, it is recommended to dose pexidartinib twice daily at least 1 h before or 2 h after a meal. Pexidartinib does not prolong the QTc interval.

1.3. Study Rationale

When administered with the FDA high-fat meal, pexidartinib exposure doubles. Currently in outpatient-based studies pexidartinib is recommended to be taken twice a day on an empty stomach, at least 1 h before or 2 h after a meal. The information derived from this study could help with providing flexibility in dosing, timing of food intake, and types of meals for subjects with tenosynovial giant cell tumor (TGCT).

1.4. Risks and Benefits for Study Subjects

There is no direct benefit for study 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 have 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 (AUC) of 491,948 ng•h/mL (1800 mg fed state) ng•h/mL. No safety signals in vital signs, physical examinations, or ECG recordings, including QT prolongation, were reported.[1] 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 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 weeks, have generally resolved with treatment discontinuation, but in rare cases have been severe, requiring liver dialysis and had a protracted course (8 mo).

2. STUDY OBJECTIVES AND HYPOTHESIS

2.1. Study Objectives

2.1.1. Primary Objectives

The primary objectives of this study are:

- To assess the effect of low-fat food on the pharmacokinetics (PK) of pexidartinib following a single oral dose of 400 mg administered in healthy subjects
- To assess the PK of pexidartinib following a single oral dose of 200 mg administered with low-fat food in healthy subjects

2.1.2. Secondary Objective

The secondary objective of this study is:

- To characterize the safety and tolerability of pexidartinib in healthy subjects following administration of a single oral dose of pexidartinib with low fat food and without food

2.2. Study Hypothesis

There is no hypothesis for this study. This study is being conducted to estimate the effect of low-fat food on pexidartinib PK.

2.3. Study Endpoints

2.3.1. Primary Endpoint

Plasma concentration time data for pexidartinib will be analyzed using noncompartmental methods. The following PK parameters will be reported: maximum observed concentration in plasma (Cmax), time to maximum observed concentration (Tmax), and area under the concentration-time curve from time of dosing to last measurable concentration (AUClast) and area under the concentration-time curve from time of dosing to infinity (AUCinf). Terminal half-life (t1/2), apparent total body clearance (CL/F), and apparent volume of distribution (Vz/F) will also be reported.

2.3.2. Secondary Endpoint(s)

Safety endpoints include ECG assessments (QT, PR, QRS, RR, and QTc [QTcB, QTcF] intervals), vital sign measurements, clinical laboratory tests, adverse events, and findings from physical examinations

2.3.3. Exploratory Endpoint

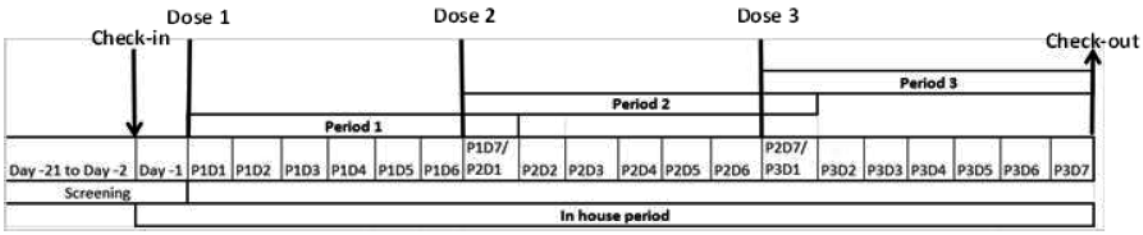
Not applicable

3. STUDY DESIGN

3.1. Overall Design

3.1.1. Overview

Figure 3.1: Schematic Chart of Study Design



3.1.2. Dose Escalation Process

Not applicable.

3.1.3. Study Stopping Criteria

Not applicable

3.2. Discussion of Study Design

4. STUDY POPULATION

4.1. Inclusion Criteria

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

1. Healthy male and female subjects between 18 and 60 years (y) of age, inclusive.
2. BMI of 18 to 30 kg/m^2, inclusive.
3. Good health as determined at Screening and Check-in by examining medical history (Screening only) and performing physical examinations, vital signs, ECGs, serum chemistry, hematology, coagulation tests (Screening only), virology (Screening only), and urinalysis.
4. Negative serum pregnancy test at Screening and during Check-in for female subjects.
5. Female subjects must be:

   - Surgically sterile (documented hysterectomy, bilateral tubal ligation, or bilateral salpingo-oophorectomy, Essure® with hysterosalpingogram [documentation to confirm tubal occlusion 12 wk after procedure])

   OR

   - Naturally postmenopausal (spontaneous cessation of menses) for at least 12 consecutive mo prior to dosing, with a follicle stimulating hormone (FSH) level at Screening of ≥40 mIU/mL

   AND

   - Nonlactating
6. Male subjects must be:

   - Surgically sterile (confirmed by documented azoospermia 90 d after the procedure)

   OR

   - Agree to use double barrier methods of contraception from Check-in until 90 d after the final dose of pexidartinib. Adequate methods of contraception for subjects or partners include: condom with spermicidal gel, diaphragm with spermicidal gel, and abstinence. If a subject is not sexually active but becomes active, he and his partner must use the above listed double barrier methods of contraception. Male subjects must not donate sperm during the study and for up to 90 d after the final dose.
7. Negative urine test for drugs of abuse (opiates, benzodiazepines, amphetamines, cannabinoids, cocaine, barbiturates, and phencyclidine), cotinine, and alcohol at Screening and Check-in.
8. Negative test result for human immunodeficiency virus (HIV) antibody, hepatitis B surface antigen (HBsAg), and hepatitis C virus (HCV) antibody at Screening.

9. Willingness to refrain from consuming food or beverages containing caffeine/xanthine or alcohol for 48 h prior to Check-in on Day -1 until the end of the study.
10. Willingness to refrain from consuming grapefruit/grapefruit juice and Seville oranges 7 d before the first dose of study drug on Day 1 until the end of the study.

4.2. Exclusion Criteria

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

1. History of any clinically significant disorder, including cardiovascular, hematologic, pulmonary, hepatic, renal, gastrointestinal, connective tissue disease, uncontrolled endocrine/metabolic, oncologic (within the last 5 y), neurologic, and psychiatric diseases, or any disorder that may prevent the successful completion of the study.
2. 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).
3. History of clinically significant neutropenia.
4. Use of any prescription medications/products and any medications known to induce or inhibit CYP and UGT enzymes within 28 d from the first dose and during the study (see Section 16.5 for a list of drug products that inhibit/induce CYP and UGT enzymes).
5. Use of food or beverages containing grapefruit 7 d prior to dosing and during the study.
6. Use of over the counter (OTC), nonprescription medication (including vitamin D preparations and calcium) within 14 d from the first dose and during the study (excluding acetaminophen ($\leq$ 2 g/d).
7. Use of supplements (including phytotherapeutic/herbal/plant-derived preparations and most vitamins and minerals) within 14 d from the first dose and during the study.
8. Use of or caffeine-containing foods or beverages within 48 h prior to Check-in and during confinement.
9. Consumption of alcohol within 48 h prior to Check-in and during confinement.
10. Laboratory results (serum chemistry, hematology, and urinalysis) outside the normal range, if considered clinically significant by the investigator. Liver function test results (ALT, AST, total bilirubin) greater than the upper limit of normal. Hemoglobin levels must be $\geq$ 11.5 g/dL for female subjects and $\geq$ 12.5 g/dL for male subjects.
11. Estimated glomerular filtration rate (eGFR) (using the Cockcroft-Gault equation) < 90 mL/min at Screening.
12. History or presence of an abnormal ECG, which, in the investigator's opinion, is clinically significant and/or a corrected QT interval using Fridericia's formula (QTcF) $\geq$ 450 msec for males and $\geq$ 470 msec for females at Screening.
13. Blood donation of 500 mL or more or a significant loss of blood within 56 days prior to the first dose.
14. Receipt of a transfusion or any blood products within 30 days prior to the first dose.

15. Current participation in another investigational study or who have participated in an investigational study within the past 30 days prior to the first dose.
16. Consumption of more than 28 units of alcohol per wk (males) or 14 units of alcohol per wk (females), where 1 unit of alcohol equals 1/2 pint of beer, 4 ounces of wine, or 1 ounce of spirits, or significant history of alcoholism or drug/chemical abuse within the last 2 y.
17. Use of tobacco products or nicotine-containing products (including smoking cessation aids, such as gums or patches) within 6 mo prior to the first dose.
18. Positive results on tests for drugs of abuse, cotinine or alcohol at Screening or Check-in.
19. Positive test result for HBsAg, HCV antibody, or HIV antibody.
20. Employment by the clinic.
21. Unable to consume or allergic to the breakfast meal
22. Any other reason, in the opinion of the investigator, that precludes subject participation in the study.
23. Familial relationship with another study participant.

Subjects must be compliant with all inclusion and none of the exclusion criteria

5. STUDY TREATMENT(S)

5.1. Assigning Subjects to Treatment Group(s) /Sequences and Blinding

5.1.1. Treatment Group(s) /Sequences

Subjects will be randomized to 1 of 6 sequences: ABC, ACB, BAC, BCA, CAB, and CBA.

The study treatments include:

- Treatment A: Single oral 400 mg (2 × 200 mg capsules) of pexidartinib in the morning with 240 mL of water after an overnight fast of 10 h
- Treatment B: Single oral 400 mg (2 × 200 mg capsules) of pexidartinib in the morning within 30 min of a low-fat standard breakfast meal
- Treatment C: Single oral 200 mg (1 × 200 mg capsule) of pexidartinib in the morning within 30 min of a low-fat standard breakfast meal

5.1.2. Method of Treatment Group(s) /Sequences Allocation

This is an open-label randomized study. The randomization schedule will be produced by a statistician from Worldwide Clinical Trials, under the specification approved by the sponsor statistician. A dummy schedule will first be produced and will be checked by the sponsor statistician. Prior to the start of the study, a copy of the randomization schedule will be supplied by the Worldwide Clinical Trials statistician to the clinical site pharmacist and at an appropriate time to the bioanalytical division at Celerion.

5.1.3. Blinding

Not applicable. This is an open-label study.

5.1.4. Emergency Unblinding Procedure

Not applicable.

5.2. Study Drug

5.2.1. Description

Pexidartinib 200 mg capsules will be provided by the sponsor in open-labeled bottles.

5.2.2. Labeling and Packaging

Pexidartinib 200 mg bottles will be labeled in compliance with regulatory requirements. The packaging will clearly display the name of the study drug, the lot number, storage condition, and other required information in accordance with local regulations.

5.2.3. Preparation

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

5.2.4. Administration

Pexidartinib will be administered orally in the clinic with approximately 240 mL of water.

The study product will be administered in accordance with the protocol. Study product will be administered only to subjects participating in the clinical study. It is a violation of the regulations to use unapproved study product for purposes other than the protocol.

The site will complete the required documentation as provided by Daiichi Sankyo, Inc. (DSI) or its representatives to document dispensing of the study products. All information will be recorded immediately on a drug dispensing form each time the study products are dispensed to a subject

5.2.5. Storage

Drug supplies must be stored in a secure, limited access storage area under the recommended storage conditions.

Pexidartinib 200 mg capsules should be stored at 20ºC to 25ºC (68 ºF to 77ºF). Excursions are permitted to 15ºC to 30ºC (59ºF to 86ºF). Capsules should not be frozen.

5.2.6. Drug Accountability

When a drug shipment is received, the investigator or designee will check the amount and condition of the study drug, check for appropriate local language in the label and supporting documentation, and sign the Receipt of Shipment Form provided. The Receipt of 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 DSI as soon as possible if there is a problem with the shipment.

A Drug Accountability Record will be provided for the pexidartinib study product. The record must be kept current and should contain the dates and quantities of drug received, each subject's identification number and/or initials or supply number as applicable, to whom the investigational medicinal product were dispensed, the date and quantity of investigational medicinal product dispensed and remaining, if from individual subject drug units as well as the initials of the dispenser.

At the end of the study, or as directed, the investigator will arrange for the destruction of unused, partially used, or empty containers of pexidartinib study product. During the site approval process, appropriate and acceptable destruction procedures will be verified. If absolutely necessary and after DSI approval, drug (used/unused) may be returned to DSI or a designee as instructed by DSI.

If in the event the investigational medicinal products are returned for some pre-approved reason, the investigational medicinal product will be returned only after the study monitor has completed a final inventory to verify the quantity to be returned. The return of investigational medicinal product must be documented, and the documentation included in the shipment. At the end of the study, a final investigational medicinal product reconciliation statement must be completed by the investigator or designee and provided to the sponsor.

All investigational medicinal product 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 supplies 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

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

5.6. Prior and Concomitant Medications

Medications used 30 d prior to Screening will be recorded.

The following medications and products will be prohibited:

- Any prescription medications/products and any medications known to induce or inhibit CYP and UGT enzymes within 28 d from the first dose and during the study (see Section 16.5 for a list of drug products that inhibit/induce CYP and UGT enzymes).
- Any OTC, nonprescription medications (including vitamin D preparations and calcium) within 14 d from the first dose and during the study. However, topical hydrocortisone will be allowed for contact dermatitis, and prune juice will be allowed for constipation.
- Use of supplements (including phytotherapeutic/herbal/plant-derived preparations and most vitamins and minerals) within 14 d from the first dose and during the study.

Acetaminophen ($\leq$ 2 g/d) is allowed during confinement at the discretion of the investigator.

Any medication (other than study drugs) taken by subjects during the course of the study will be recorded and coded using the World Health Organization (WHO) dictionary. If drug therapy other than that specified by the protocol is taken, a joint decision will be made by the investigator and sponsor whether to continue or discontinue the subject.

5.6.1. Dietary and Lifestyle Restrictions

At Screening, subjects will be informed that if accepted for the study, no foods or beverages containing grapefruit is allowed for 7 d prior to dosing and throughout the study, and alcohol is

prohibited for 48 h prior to Check-in and during confinement. Subjects must also agree to abstain from caffeine-containing foods or beverages from 48 h prior to Check-in and during confinement.

Treatment A:

Subjects will be required to fast overnight for at least 10 h prior to dosing.

Treatment B and Treatment C:

Subjects will be required to fast overnight for at least 10 h until 30 min prior to dosing, when they will be given a standard low-fat breakfast which will be entirely consumed within 30 min. The breakfast will consist of 8 ounces of 1 percent fat milk, 1 boiled egg, and one packet of instant flavored oatmeal made with water.

Subjects should be dosed within 5 minutes of completing the meal.

For all treatments:

Following dosing, subjects will be required to fast for at least 4 h. A standard menu and meal schedule (based on United States Recommended Daily Allowance) will be administered uniformly to all subjects. Meals and/or snacks will be served at appropriate times following dosing. Identical meals will be served for each treatment (except for the test breakfast). The calorie content, as well as the percent of calories from protein, carbohydrate, and fat, will be uniform for each meal during the study (ie, breakfast uniform to breakfast, lunch uniform to lunch).

Water will not be permitted from 1 h before until 2 h after dosing (with the exception of 240 mL of water administered with dosing and the liquid given with breakfast), but will be allowed at all other times.

Except when ECGs must be taken in supine position, subjects will remain seated in an upright position with minimal ambulation (ie, only to and from the washroom or for study procedures) for the first 4 h following dosing. When ECGs assessment and PK samples are scheduled at the same time, ECG will be done first followed by PK sampling.

5.7. Subject Withdrawal/Discontinuation

5.7.1. Reasons for Withdrawal

Any subject who discontinues from the study treatment for any reason will have their study treatment discontinuation recorded.

Following randomization, subjects may be withdrawn before completing the study per protocol for any of the following reasons:

- AE
- Withdrawal of consent by subject
- Physician decision
- Pregnancy

- Protocol deviation
- Study terminated by sponsor
- Other

All subjects who are withdrawn from the study should complete protocol specified withdrawal procedures (Section 6.6).

5.7.2. Withdrawal Procedures

In accordance with the Declaration of Helsinki and other applicable regulations, a subject has the right to withdraw from the study at any time and for any reason without prejudice to his or her future medical care by the study physician or at the study site.

If a subject withdraws from the study, s/he will be required to have Early Termination study procedures performed (refer to Section 6.6).

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

There is no plan for subject replacement.

5.7.1. Subject Re-screening Procedures

Not applicable.

5.8. Criteria for Suspending Study Treatment

Not applicable.

6. STUDY PROCEDURES

6.1. Screening

Screening will be conducted anytime within 21 d prior to dosing. Informed consents (general study procedures/genotyping and the Health Insurance Portability and Accountability Act [HIPAA][4]) will be obtained from the subject prior to performing any of the Screening assessments.

The following activities and/or assessments will be performed at Screening:

- Informed consent
- Inclusion/exclusion criteria
- Medical history
- Prior and concomitant medication history
- Complete physical exam
- Height and body weight (and BMI calculation)
- 12-lead ECG
- Vital signs (blood pressure, heart rate, oral temperature, and respiratory rate)
- Blood samples for:
  - HIV antibody
  - HBsAg and HCV antibodies
  - Clinical laboratory tests (hematology and fasting serum chemistry); subjects will fast for approximately 10 h prior to Screening for the serum chemistry tests
  - Coagulation tests (prothrombin time [PT] / INR and activated partial thromboplastin time [aPTT])
  - Serum pregnancy test for all females
  - FSH test for naturally postmenopausal female subjects
- Urine samples for:
  - Urine drug screen (opiates, benzodiazepines, amphetamines, cannabinoids, cocaine, barbiturates, phencyclidine), cotinine, and alcohol
  - Clinical laboratory tests (urinalysis)
- Calculation of eGFR (using the Cockcroft-Gault equation)

6.2. Subject Management

Not applicable.

6.3. Randomization

On Day -1 of Period 1, following the review of the safety laboratory assessments and 12-lead ECG measurements, randomization numbers will be assigned to subjects without regard to the randomization schedule. A subject is considered randomized once he/she receives the first dose.

No subject will be replaced.

More information on the method of assigning subjects is found in Section 5.1.2.

6.4. Treatment Period

6.4.1. Day -1 of Period 1 Check-in

A sufficient number of alternate subjects will be brought into the clinic at Check-in (Day -1) of Period 1. Alternate subjects will undergo all baseline assessments. In the event that a subject scheduled to be randomized cannot be dosed, an alternate subject will be assigned the same randomization number and sequence of treatments.

The following procedures will be carried out at Check-in:

- Admission to clinic
- Inclusion/exclusion criteria
- Abbreviated medical history (applicable to Period 1 only, since Screening) and concomitant medication history
- Complete physical exam
- Body weight
- Blood samples for:
  - Clinical laboratory tests (hematology and fasting serum chemistry); subjects will fast for approximately 10 h prior to Check-in for the serum chemistry tests
  - Serum pregnancy test for all females
- Urine samples for:
  - Drug screen (opiates, benzodiazepines, amphetamines, cannabinoids, cocaine, barbiturates, phencyclidine), cotinine, and alcohol
  - Clinical laboratory urinalysis tests

6.4.2. Day 1

The following procedures will be performed on Day 1 of each period:

- Administration of pexidartinib according to the randomization scheme at Time 0; for Treatment A, subjects will fast for approximately 10 h prior to dosing; for Treatment B and Treatment C, subjects will fast for approximately 10 h then consume a standard low-fat meal starting 30 min before dosing.

- Vital signs (blood pressure, heart rate, oral temperature, and respiratory rate) prior to dosing and at approximately 2 h postdose
- 12-lead ECGs prior to dosing and at approximately 2 h postdose
- Blood samples for:
  - PK analysis prior to dosing and at 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 8, 10, 12, 14, and 22 h postdose
- Continuous monitoring of AEs, starting from dosing, and concurrent medication

6.4.3. Day 2

The following procedures will be performed on Day 2 of each period:

- Vital signs (blood pressure, heart rate, oral temperature, and respiratory rate) at approximately 24 h postdose
- 12-lead ECGs at approximately 24 h postdose
- Blood samples for PK analysis at 24, 28, 32, and 36 h postdose
- Continuous monitoring of AEs and concurrent medication

6.4.4. Day 3

The following procedures will be performed on Day 3 of each period:

- Blood samples for PK analysis at 48, 54, and 60 h postdose
- Continuous monitoring of AEs and concurrent medication

6.4.5. Day 4

The following procedures will be performed on Day 4 of each period:

- Blood samples for PK analysis at 72 and 84 h postdose
- Continuous monitoring of AEs and concurrent medication

6.4.6. Day 5

The following procedures will be performed on Day 5 of each period:

- Blood samples for PK analysis at 96 and 108 h postdose
- Continuous monitoring of AEs and concurrent medication

6.4.7. Day 6

The following procedures will be performed on Day 6 of each period:

- Blood samples for PK analysis at 120 and 132 h postdose
- Continuous monitoring of AEs and concurrent medication

6.4.8. Day 7

The following procedures will be performed on Day 7 of each period:

- Vital signs (blood pressure, heart rate, oral temperature and respiratory rate) at approximately 144 h postdose
- 12-lead ECGs at approximately 144 h postdose
- Blood sample for PK analysis at 144 h postdose
- Continuous monitoring of AEs and concurrent medication

6.5. Washout

There will be a washout of at least 6 d between each dose of pexidartinib.

6.6. Check-out or Early Termination

The following procedures will be performed at check-out of Period 3 (Day 7) or upon Early Termination:

- Complete physical exam
- Body weight
- Vital signs (blood pressure, heart rate, oral temperature, and respiratory rate), if not already taken
- 12-lead ECGs, if not already taken
- Blood samples for:
  - Clinical laboratory tests (hematology and fasting serum chemistry); subjects will fast for approximately 10 h prior to check-out for the serum chemistry tests
  - Serum pregnancy test for all females
- Urine samples for clinical laboratory urinalysis tests
- Continuous monitoring of AEs and concurrent medication

6.7. Follow-up

If a subject is withdrawn from the study due to an AE, the subject will be asked to complete, at a minimum, assessments of the early withdrawal visit. If the AE has still not resolved, additional follow-up will be conducted, as appropriate, based on the investigator's judgment, and documented in the subject's medical records. At a minimum, serious adverse events (SAEs) should be followed for 30 d after the subject's last dose of study drug.

7. PHARMACOKINETIC ASSESSMENTS

7.1. Pharmacokinetic Assessment(s)

Pharmacokinetic analysis will be conducted in compliance with DSI's noncompartmental analysis guidelines.

The plasma concentration-time data will be analyzed using actual dosing and sampling time points using noncompartmental methods. The PK parameters listed in Table 7.1 will be calculated for pexidartinib from the individual plasma concentrations using a noncompartmental approach. Pharmacokinetic variables will be computed using WinNonlin Professional or other appropriate software.

Table 7.1: Plasma Pharmacokinetic Variables

Parameter	Units	Description
Cmax	ng/mL	Maximum observed plasma drug concentration
Tmax	h	Time of maximum observed concentration
AUClast	ng·h/mL	Area under the plasma concentration-time curve, from time 0 to the last measurable concentration (Clast), as calculated by the log-linear trapezoidal method
AUCinf	ng·h/mL	AUC from the time of dosing extrapolated to infinity, calculated as: AUCinf = AUClast + Clast/λ_Z, where λ_Z is the apparent terminal elimination rate constant calculated by linear regression of the terminal linear portion of the log concentration versus time curve
AUCextr%	%	Percentage of AUCinf that is extrapolated from tlast to infinity, calculated as: 100×[1-(AUClast/AUCinf)], where tlast is the time of the last measurable plasma drug concentration
t1/2	h	Terminal elimination half-life, calculated as: $ln(2)/\lambda_Z$
CL/F	L/h	Apparent total body clearance, calculated as: Dose/AUC
Vz/F	L	Apparent volume of distribution, calculated as: Dose/AUCinf × λ_Z

A more detailed description of the pharmacokinetic assessments will be provided separately in the SAP.

7.2. Pharmacodynamic (PD) Assessment (s)

Not applicable.

7.3. Immunogenicity

Not applicable.

8. SAFETY EVALUATION AND REPORTING

8.1. Assessment of Safety Endpoint Event(s)

The safety endpoints include AEs, physical examination, vital signs, 12-lead ECGs, and clinical laboratory tests (standard hematology, serum chemistry including AST/ALT, coagulation, and urinalysis).

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 last dose of study drug (ie, Period 3 dosing), whether observed by the investigator or reported by the subject, will be recorded on the Adverse Event CRF 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, 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 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. Adverse events 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

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.

Based on pooled data from 424 subjects who received pexidartinib, elevations of liver transaminases (up to Grade 3) and bilirubin have been observed in studies with pexidartinib, together with cases of drug-induced cholestasis. All these events occurred in subjects treated with pexidartinib in a continuous, multiple dose regimen. Cases of cholestasis have been observed in the first 8 wk, have generally resolved with treatment discontinuation, but in rare cases have been severe, requiring liver dialysis and had a protracted course (8 mo).

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, Oct 1994).

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

A 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, Oct 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 (NCI) 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 is a known reaction to the drug under study or its chemical group or 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, and concomitant medications).

8.4.5. Action Taken Regarding Study Drug(s)

- Dose Not Changed: No change in study drug dosage was made.
- Drug Withdrawn: The study drug was permanently stopped.
- Not Applicable: Subject died, study treatment had been completed prior to reaction/event, or reaction/event occurred prior to start of treatment.

8.4.6. Other Action Taken for Event

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

8.4.7. 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, SAEs will be reported in the CRF.

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 (see Section 8.4.2 for definition)

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

SAEs and AESIs (Section 8.3) 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 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 CSPV-Clinical@dsi.com. See Section 14.10.5 for contact information for SAE reporting. Please call the local SAE Hotline or your study monitor for any questions on SAE reporting.

8.6. Notifying Regulatory Authorities, Investigators, and Institutional Review Board/Ethics Committee

DSI and/or Worldwide Clinical Trials Early Phase Services, LLC will inform investigators, Institutional Review Boards/Ethics Committees (IRBs/ECs), and regulatory authorities of any Suspected Unexpected Serious Adverse Reactions (SUSARs) occurring in other studies of the investigational drug, as appropriate per local reporting requirements. DSI and/or CRO 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 Early Termination 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 for both drug safety and public health concerns. It is the responsibility of the investigator, or designee, to report any pregnancy in a female subject 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 a 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

Clinical laboratory tests (hematology, serum chemistry, and urinalysis) will be performed at Screening, Check-in of Period 1 and at Check-out of Period 3 or Early Termination.

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, alkaline phosphatase, 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) will be performed at Screening only. Approximately 2.7 mL of blood will be withdrawn for these tests.

8.9. Vital Signs

Resting vital signs will be taken after at least 10 min in a supine position.

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 postdose in each study period, 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 within 2 h prior to the dose.

Body weight and height will be recorded at Screening. Body weight will also be recorded at Check-in to Period 1 and at Check-out of Period 3 or Early Termination. BMI will be calculated at Screening.

Information will be entered in the CRF on whether or not measured, date of measurement, and measurement results for the following items: systolic blood pressure, diastolic blood pressure, pulse, respiratory rate, body temperature, height, body weight, and BMI.

8.10. Electrocardiograms

ECGs will be read on site as part of the safety assessments.

12-lead ECGs will be performed at Screening, predose, and at 2, 24 and 144 h postdose, or Early Termination.

Subjects should be lying quietly in a fully supine position for at least 10 min prior to each 12 lead ECG recording.

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 within 2 h prior to the dose.

8.11. Physical Examinations

A complete physical examination will be performed at Screening. A complete physical examination will be performed at Check-in to Period 1 and at check-out of Period 3 or Early Termination. A medically qualified person will perform the physical exam. The physical examination will include the examination of the following body systems: respiratory, cardiovascular, gastrointestinal, dermatological, musculoskeletal, psychiatric, neurologic, and 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 to Period 1 and Check-out of Period 3 or Early Termination. Dosing on Day 1 of Period 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

Not applicable.

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 summarized using descriptive statistics.

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

Extra measurements (such as unscheduled or repeat safety assessments) will not be included in the descriptive statistics, but will be included in subject listings.

10.2. Analysis Sets

10.2.1. Pharmacokinetic Analysis Set

The PK analysis set includes all subjects who receive at least 1 dose of pexidartinib and have sufficient samples to adequately assess the PK parameters. The impact of clinically significant events that may affect the estimation of PK parameters will be assessed while analyzing data and handled appropriately. Any exclusion will be clearly delineated in the report. Individual plasma concentrations for all subjects will be reported.

10.2.2. Safety Analysis Set

The safety analysis set includes all subjects who receive at least 1 dose of pexidartinib.

10.3. Study Population Data

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

Medical history data will also be summarized.

10.4. Statistical Analysis

10.4.1. Pharmacokinetic Analyses

All PK analyses will be based on the PK analysis set.

Individual plasma concentration-time data will be presented graphically by treatment and actual time points using linear and semilog scales. Mean (SD) plasma concentration-time data will be presented graphically for pexidartinib by nominal time points using linear and semi-log scales.

If a subject vomits within a period of time equal to two times the median Tmax of pexidartinib, statistical analysis will be performed with and without data from the period subject vomited in.

Log-transformed Cmax, AUClast, and AUCinf of pexidartinib will be analyzed using a mixed effect analysis of variance (ANOVA) model with treatment, period, and sequence as fixed effects and subject nested within sequence as a random effect. The point estimates of ratios of central values for Treatments B versus A, will be calculated by exponentiation of the differences in the least squares means (logarithm-transformed data) between the treatments, Treatment B (400 mg pexidartinib administered with a low-fat meal) versus Treatment A (Reference, 400 mg pexidartinib in the fasted state).The 2-sided 90% confidence intervals (CIs) will be calculated similarly by exponentiation of the corresponding 2 sided 90% for the difference between the least squares means calculated for the ln transformed values.

A more detailed description of the planned pharmacokinetic analysis will be provided separately in the SAP.

10.4.2. Pharmacodynamic Analyses

Not applicable.

10.4.3. Safety Analyses

All safety analyses will be based on the safety analysis set.

10.4.3.1. Adverse Event Analyses

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) coding dictionary. All AEs including serious AEs will be mapped to system organ class 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 TEAE will be tabulated for the safety set by MedDRA system organ class and preferred term with a breakdown by treatment, and further by relationship (related / not related) to study drug administered and by Common Terminology Criteria (CTC) AE grade.[5] An AE that emerges or worsens in severity during a washout period will be counted as a TEAE toward the treatment in the preceding period. Listings of deaths, SAEs, and AEs that lead to discontinuation of a subject will be presented.

10.4.3.2. Clinical Laboratory Evaluation Analyses

Hematology, serum chemistry, and urinalysis, at each planned assessment will be summarized for the safety analysis set by treatment. Shift tables (CTCAE grade of the worst value) will also be provided by treatment. Subjects with abnormal values will be noted in the data listings.

10.4.3.3. Vital Sign Analyses

Vital sign evaluations at each planned assessment and change in vital sign values from baseline at each planned post-baseline assessment will be summarized for the safety analysis set by treatment.

Oral temperature and respiratory rate will not be statistically analyzed. Data listings for oral temperature and respiratory rate will be described as appropriate by subject and treatment.

10.4.3.4. Electrocardiogram Analyses

The ECG parameters (PR, RR, QRS, and QT intervals, and QTcB, and QTcF intervals where the QT intervals correct for heart rate by the Bazett's and Fridericia's formula (QTcB = QT/[RR]1/2 and QTcF = QT/[RR]1/3 respectively) will be summarized by treatment.

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

10.4.3.5. Physical Finding Analyses

Physical examination data at each evaluation will be listed.

10.4.3.6. Other Safety Analyses

Not applicable.

10.5. Sample Size Determination

Twenty-four subjects will be randomized, with the expectation that at least 21 will complete all 3 periods of the study. Discontinued subjects will not be replaced. The sample size is not determined based on statistical considerations, but to obtain adequate precision for the estimation. Based on the results from Study PL3397-A-U114, the intra-individual variability (intra-individual CV%) in this study is assumed to be around 30%. With a sample size of 21 and assumed coefficient of variation (CV) of 30%, a 30% or higher increase in geometric mean ratio of exposures between Treatment A and B can be determined with an imprecision of 15% (distance between the mean ratio and the lower bound of CI) when the 90% CIs are generated.

10.6. Statistical Analysis Process

To preserve the integrity of the statistical analysis 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 investigator/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 WCT 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, CRFs, source data, and other pertinent documents).

The verification of adherence to the protocol; completeness, accuracy, and consistency of the data; and adherence to ICH 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 CRFs 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 CRFs. Detailed information is provided in the monitoring plan.

The monitor will communicate deviations from the protocol, SOPs, 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 all subjects who received at least one dose of study medication. 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 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.

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 Worldwide Clinical Trials. Data will be vetted both electronically and manually for CRFs 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 Adverse Events will be coded using MedDRA (latest version). Prior and concomitant medication entered into the database will be coded using the WHO Drug Dictionary (latest version).

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 CRFs 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, date and outcome 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 CRF 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, CRFs, inventory of study drug, regulatory documents (eg, protocol and amendments, IRB/EC 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. Trial Master File includes:

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

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

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.

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 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 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 the sponsor. 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 International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) consolidated Guideline E6 for Good Clinical Practice (GCP) (CPMP/ICH/135/95), and applicable regulatory requirement(s) including the following:

- European Commission Directive (2001/20/EC Apr 2001) and/or;
- European Commission Directive (2005/28/EC Apr 2005) and/or;
- US Food and Drug Administration (FDA) GCP Regulations: Code of Federal Regulations (CFR) Title 21, parts 11, 50, 54, 56, and 312[3] as appropriate and/or;
- Japanese Ministry of Health, Labor and Welfare Ordinance No. 28 of 27 March, 1997; and/or
- 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 CRFs 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(s), and the IRB/EC 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 drugs are 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 or EC 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 CRF.

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 (genomic, 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 HIPAA.[4] 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 Investigator's Brochure, 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 or EC 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 must submit and, where necessary, obtain approval from the IRB or EC for all subsequent protocol amendments and changes to the ICF. The investigator should notify the IRB or EC 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(ies) 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 Sponsor and, if required, by the regulatory authority(ies), and which was given approval/favorable opinion by the IRBs/ECs.

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. 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, IRBs/ECs, 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/EC. 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 DSI or the CRO. 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/EC 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

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

14.10.2. Sponsor's Clinical Study Manager

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

14.10.3. Sponsor's Pharmacokinetics Reviewer

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

14.10.4. Sponsor's Medical Monitor

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

14.10.5. Sponsor's Safety Contacts

Daiichi Sankyo Pharma Development
Clinical Safety and Pharmacovigilance
Email to: CSPV-Clinical@dsi.com

14.10.6. EDC Vendor

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

14.10.7. Bioanalytical Vendor

[redacted]
Bioanalytical Principal Investigator

Celerion
621 Rose Street
Lincoln, NE 68502
[redacted]

[redacted]
www.celerion.com

14.10.8. Central Laboratory

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

14.10.9. Sponsor's Biostatistician

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

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
[redacted]

14.10.11.1.CRO Investigator

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

14.10.11.2.CRO Project Manager

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

15. REFERENCES

1. Pexidartinib Investigator's Brochure, Version 10.0, 19 Dec 2018.
2. West RB, Rubin BP, Miller MA, et al. A landscape effect in tenosynovial giant-cell tumor from activation of CSF1 expression by a translocation in a minority of tumor cells. Proc Natl Acad Sci U S A. 2006;103(3):690-695.
3. Food and Drug Administration: Code of Federal Regulations (CFR). Available at http://www.gpoaccess.gov/cfr
4. US Health Insurance Portability and Accountability Act (HIPAA). 21 Aug 1996. http://aspe.hhs.gov/admnsimp/pl104191.htm
5. National Cancer Institute Common Terminology Criteria for AEs, version 5.0, published 27 Nov 2017. Available at: https://ctep.cancer.gov/protocoldevelopment/electronic_applications/ctc.htm#ctc_50

16. APPENDICES

16.1. Labeling and Packaging

Not applicable

16.2. Blood Collection Volume by Category and Total

Table 16.1: Blood Collection Volumes

Test		Volume per Test (mL)	No. of Time Points per Subject	Total Volume per Test (mL)	
Screening	Serum chemistry, HIV antibody, HBsAg, HCV antibody, FSH if applicable, serum pregnancy	8.5	1	8.5	
	Hematology	4.0	1	4.0	
	Coagulation (PT/INR and aPTT)	2.7	1	2.7	
Serum chemistry, serum pregnancy, if applicable		8.5	2	17.0	
Hematology		4.0	2	8.0	
PK pexidartinib			2.0	91	182.0
Total:			-	**95**	**222.2**

Abbreviations: aPTT = activated partial thromboplastin time; FSH = follicle stimulating hormone; HBsAg = hepatitis B surface antigen; HCV = hepatitis C virus; HIV = human immunodeficiency virus; INR = international normalized ratio; PK = pharmacokinetic; PT = prothrombin time
Notes: Blood collection in subjects with adverse events should be continued until resolution of the events (even after the scheduled observation period). Blood collection to be used for several different tests but taken at one time is counted as one collection.

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 16.6).

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
Phone: (402) 437-4849

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. Example:

- 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 for sample receipt is:

Celerion
621 Rose Street
Lincoln, NE 68502
[redacted]

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. Cytochrome P450 Clinically Significant Drug Interaction Table

List obtained from P450 Drug Interaction Table: Abbreviated "Clinically Relevant" Table, Version 5.0 released on January 12, 2009, last updated on 12 Jul 2013. Available at: http://medicine.iupui.edu/clinpharm/DDIs/ClinicalTable.aspx.

INHIBITORS			
1A2	**2B6**	**2C8**	**2C19**
amiodarone cimetidine efavirenz fluoroquinolones fluvoxamine ticlopidine	clopidogrel thiotepa ticlopidine voriconazole	gemfibrozil montelukast	cimetidine esomeprazole felbamate fluoxetine fluvoxamine isoniazid ketoconazole lansoprazole omeprazole oral contraceptives pantoprazole ticlopidine voriconazole

INHIBITORS			
2C9	**2D6**	**2E1**	**3A4,5,7**
amiodarone efavirenz fluconazole isoniazid metronidazole paroxetine sulfamethoxazole voriconazole	bupropion fluoxetine paroxetine quinidine1 duloxetine amiodarone cimetidine aripiprazole diphenhydramine chlorpheniramine clomipramine doxepin haloperidol methadone ritonavir terbinafine	disulfiram	HIV antivirals: indinavir nelfinavir ritonavir clarithromycin itraconazole ketoconazole nefazodone erythromycin grapefruit juice verapamil2 suboxone diltiazem cimetidine amiodarone NOT azithromycin fluvoxamine troleandomycin voriconazole

UGT INHIBITORS			
valproic acid probenecid			
INDUCERS			
1A2	**2B6**	**2C8**	**2C19**
carbamazepine chargrilled meat rifampin tobacco	artemisinin carbamazepine efavirenz nevirapine phenobarbital phenytoin rifampin	N/A	efavirenz rifampin ritonavir St. John's Wort
INDUCERS			
2C9	**2D6**	**2E1**	**3A4,5,7**
carbamazepine nevirapine phenobarbital rifampin St. John's Wort	N/A	isoniazid	carbamazepine efavirenz nevirapine phenobarbital phenytoin pioglitazone rifabutin rifampin St. John's Wort troglitazone

16.6. Schedule of Events

Table 16.2: Schedule of Events (Screening through Day1)

Study Period →	**Screening[a]**	**Period 1**	**Periods 1, 2, and 3[b]**																		
Study Day[c] →	**-21 to -2**	**Check-in[d] -1**	**1**																		
Study Event ↓ Study Hour →			pre-dose	0	0.5	1	1.5	2	2.5	3	3.5	4	4.5	5	6	8	10	12	14	22
Informed consent	X																			
Inclusion/exclusion criteria	X	X																		
Medical/medications history	X	X																		
Complete physical exam	X	X																		
Body weight	X	X																		
Height and BMI	X																			
Randomization[e]																				
Drug, cotinine, alcohol screen	X	X																		
Virology	X																			
Serum pregnancy test	X	X																		
FSH level[f]	X																			
Hematology, serum chemistry, urinalysis[h]	X	X																		
Coagulation	X																			
12-lead ECGs	X		X					X												
Vitals (BP, HR, temp, RR)	X		X					X												

Abbreviations: AE = adverse event; BMI = body mass index; BP = blood pressure; d= day; ECG = electrocardiogram; FSH = follicle stimulating hormone; h = hour; HR = heart rate; PK = pharmacokinetic; RR = respiratory rate; temp = oral temperature

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

[b] There will be at least a 6-d washout between the dose administered in Period 1 and that in Period 2, and the dose administered in Period 2 and that in Period 3. Periods 2 and 3 will start after the last PK sample of the previous dose from Period 2 and 3, respectively.
[c] Study days are representation of days in each period.
[d] Subjects will check in on Day -1 of Period 1 and remain confined until the end of Period 3 or Early Termination.
[e] On Day -1 of Period 1 only, following the review of safety laboratory results and ECGs, randomization numbers will be assigned to subjects. A subject is considered randomized once he/she receives the dose.
[f] FSH will be measured for naturally postmenopausal female subjects.
[g] A genotyping blood sample will be collected on Day 1 of Period 1 only, after randomization (i.e. dosing).
[h] Time windows for blood draws are:

- -2h for samples collected as pre-dose
- ±5 mins for samples collected ≤ 4 h postdose
- ±10 mins for samples collected >4h and ≤ 12 h postdose
- ±30 mins for samples collected >12h and ≤ 72 h postdose
- ±4 hours for samples collected >72 h and < 7 days postdose
- ±1 day for samples collected ≥7 days postdose

Table 16.3: Schedule of Events (Days 2 to Check of Period 3 or Early Termination)

Study Period →	**Periods 1, 2, and 3[a]**														**Check-out of Period 3 or Early Termination**
Study Day[b] →	**2**				**3**			**4**		**5**		**6**		**7**	
Study Event ↓ Study Hour →	24	28	32	36	48	54	60	72	84	96	108	120	132	144	
Complete physical exam															X
Body weight															X
Serum pregnancy test															X
Hematology, serum chemistry, urinalysis															X
12-lead ECGs	X													X	X[c]
Vitals (BP, HR, temp, RR)	X													X	X[c]
PK blood collections	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
AE monitoring	<---------- X ---------->														
Record of concomitant medication	<---------- X ---------->														
Confinement	<---------- X ---------->														

Abbreviations: AE = adverse event; BP = blood pressure; ECG = electrocardiogram; d = day; h = hour; HR = heart rate; PK = pharmacokinetic; RR = respiratory rate; temp = oral temperature

[a] There will be at least a 6-d washout between the dose administered in Period 1 and that in Period 2, and the dose administered in Period 2 and that in Period 3. Periods 2 and 3 will start after the last PK sample of the previous dose from period 2 and 3, respectively.

[b] Study days are representation of days in each period.

[c] If not already taken.