CLINICAL STUDY PROTOCOL

A PHASE 1 STUDY OF SINGLE AGENT PEXIDARTINIB IN ASIAN SUBJECTS WITH ADVANCED SOLID TUMORS

PL3397-A-A103

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DAIICHI SANKYO

INVESTIGATOR AGREEMENT

A PHASE 1 STUDY OF SINGLE AGENT PEXIDARTINIB IN ASIAN SUBJECTS WITH ADVANCED SOLID TUMORS

Sponsor Approval:

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

[redacted]	
Print Name	**Signature**
Clinical Study Lead	
Title	**Date (DD MMM YYYY)**

Investigator's Signature:

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

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

I agree to conduct this study according to this protocol and to comply with its requirements, subject to ethical and safety considerations and guidelines, and to conduct the study in accordance with the Declaration of Helsinki, International Council for Harmonisation 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.

<<Insert Name>>	
Print Name	**Signature**
<<Insert Title>>	
Title	**Date (DD MMM YYYY)**

PROTOCOL SYNOPSIS

Protocol Number:	PL3397-A-A103
Investigational Product:	PLX3397
Active Ingredient(s)/INN:	Pexidartinib
Study Title:	A Phase 1 Study of Single Agent Pexidartinib in Asian Subjects With Advanced Solid Tumors
Study Phase:	Phase 1
Indication Under Investigation:	Pexidartinib will be evaluated in subjects with advanced solid tumors.
Study Objectives:	Primary Objectives: • To assess the safety and tolerability of pexidartinib in Asian subjects with advanced solid tumors • To determine the recommended Phase 2 dose (RP2D) of pexidartinib in Asian subjects with advanced solid tumors Secondary Objectives: • To assess the pharmacokinetics (PK) profile of pexidartinib and its metabolite • To assess the pharmacodynamics (PD) effect of pexidartinib on CSF-1 and adiponectin in plasma • To evaluate the preliminary efficacy of pexidartinib • To evaluate objective response rate (ORR) (the sum of complete response [CR] rate and partial response [PR] rate) • To evaluate disease control rate (DCR) (the sum of CR rate, PR rate, and stable disease [SD] rate) • To evaluate response duration • To evaluate duration of SD • To evaluate time to response • To evaluate percentage of change in target lesion(s) Exploratory Objectives: • To explore the effect of UGT1A4 genotype on pexidartinib PK

	• To explore any possible correlation of genomics to pexidartinib safety
Study Design:	This is a Phase 1, non-randomized, open-label, multiple-dose study of pexidartinib in Asian subjects with advanced solid tumors. The study will be conducted in a dose-escalation 3+3 design. This study comprises 2 dose levels (Cohort 1 and Cohort 2) to assess the safety and tolerability, RP2D, PK and PD, and preliminary antitumor activity of pexidartinib. • Cohort 1: 600 mg/d (200 mg in the morning, 400 mg in the evening) • Cohort 2: 1000 mg/d (400 mg in the morning and 600 mg in the evening) for the first 2 weeks. Thereafter, the dose will be reduced to 800 mg/d (400 mg in the morning and 400 mg in the evening).
Study Duration:	First subject enrolled: 2Q 2016 Last subject last visit (including follow-up): approximately 2020 Subjects who continue to derive clinical benefit from treatment in the absence of subject's consent withdrawal, disease progression, or unacceptable toxicity may continue another cycle of treatment at the investigator's discretion.
Study Centers and Location:	One study site in Taiwan is planned.
Subject Eligibility Criteria:	Inclusion Criteria: Subjects must satisfy all of the following criteria to be included in the study: 1. Age should be ≥ 20 years. 2. Subjects must have a pathologically documented solid tumor that has relapsed from, or is refractory to standard treatment, or for which no standard treatment is available. 3. Women of childbearing potential must have a negative serum pregnancy test within the 14-day period prior to treatment allocation. 4. Men and women of childbearing potential are permitted in the study as long as they consent to avoid getting their partner pregnant or becoming pregnant

themselves, respectively, by using a highly effective contraception method, as described below, throughout the study and for up to 90 days after completion. Highly effective methods of contraception include hormonal methods associated with inhibition of ovulation, intra-uterine device, surgical sterilization (including partner's vasectomy), or sexual abstinence.

5. Women of non-childbearing potential may be included if they are either surgically sterile or have been postmenopausal for ≥ 1 year. Women who have documentation of at least 12 months of spontaneous amenorrhea and have a follicle-stimulating hormone (FSH) level > 40 mIU/mL will be considered postmenopausal.
6. All associated toxicity from previous cancer therapy must have been resolved (to ≤ Grade 1 or baseline) prior to administration of pexidartinib.
7. Eastern Cooperative Oncology Group Scale of Performance Status (ECOG PS) of 0 or 1.
8. Life expectancy ≥ 3 months, in the opinion of the investigator.
9. Adequate hematologic, hepatic, and renal function defined by:
    - Absolute neutrophil count ≥ 1.5×10^9/L
    - Platelet count ≥ 100×10^9/L
    - Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) ≤ 1.5 × upper limit of normal (ULN) (if liver metastases are present or subjects with hepatocellular carcinoma, ≤ 3 × ULN)
    - Albumin ≥ 3 g/dL
    - Total bilirubin ≤ 1.5 × ULN
    - Hemoglobin > 9 g/dL
    - Serum creatinine ≤ 1.5 × ULN or calculated creatinine clearance > 60 mL/min using the Cockcroft-Gault formula
10. Adequate treatment washout period before registration defined as:
    - Major surgery: ≥ 4 weeks (2 weeks for less

invasive surgery, such as colostomy)

- Radiation therapy (eg, whole brain radiotherapy): ≥ 4 weeks (if palliative stereotactic radiation therapy, ≥ 2 weeks)
- Chemotherapy or immunotherapy (including targeted therapy with antibody or small molecule, retinoid therapy, and hormonal therapy): 4 weeks or 5 half-lives of the agent, whichever is shorter (if the regimen has contained nitrosoureas or mitomycin C, ≥ 6 weeks)
- Other investigational drug therapy: ≥ 4 weeks

11. Willingness and ability to provide written informed consent prior to any study-related procedures and to comply with all study requirements.

Exclusion Criteria

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

1. Refractory nausea and vomiting, malabsorption, external biliary shunt, or significant small bowel resection that would have precluded adequate absorption.
2. Presence of a medical or psychiatric condition that, in the opinion of the investigator, made the subject inappropriate for inclusion in this study.
3. Previous use of pexidartinib or any biologic treatment targeting colony stimulating factor-1 (CSF-1) or the receptor for colony-stimulating factor-1 (CSF1R); previous use of oral tyrosine kinase inhibitors, eg, imatinib or nilotinib, is allowed.
4. Clinically active primary central nervous system tumors or brain metastasis, defined as untreated and symptomatic, or requiring therapy with steroids or anticonvulsants to control associated symptoms.
5. Active or chronic infection with hepatitis C or known positive hepatitis B surface antigen, or known active or chronic infection with human immunodeficiency virus.
6. Known active tuberculosis.

	7. Women who are breastfeeding. 8. A screening Fridericia corrected QT interval (QTcF) ≥ 450 ms (men) or ≥ 470 ms (women). 9. A medical history or complications of clinically significant lung disease (eg, interstitial pneumonia, pneumonitis, pulmonary fibrosis, and severe radiation pneumonitis). 10. A history of symptomatic congestive heart failure ([CHF]; New York Heart Association [NYHA] Classes II to IV) or serious cardiac arrhythmia requiring treatment. 11. A history of myocardial infarction or unstable angina within 6 months before enrollment. 12. An uncontrolled infection requiring intravenous injection of antibiotics, antivirals, or antifungals.
Dosage Form, Dose and Route of Administration:	Pexidartinib, as a 200-mg capsule formulation for oral administration. Pexidartinib will be taken twice daily (BID) approximately 12 hours (h) apart in the morning and evening. Doses will be taken in the fasting state (no food for 1 h before and 2 h after dosing, with a low-fat snack if needed). Each cycle of treatment will be 28 days in duration. The cycle of treatment will be continued until disease progression, unacceptable toxicity, or consent withdrawal.
Planned Sample Size:	9 to 15 subjects
Statistical Analyses:	<u>Key Safety Parameters:</u> Safety parameters will include dose-limiting toxicities (DLTs), serious adverse events (SAEs), treatment-emergent adverse events (TEAEs), physical examination findings (including ECOG PS), vital sign measurements, standard clinical laboratory parameters, electrocardiogram (ECG) parameters, and ECHO/MUGA findings. All TEAEs will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Event (NCI-CTCAE) Version 4.0. <u>Key Pharmacokinetic Parameters:</u> Plasma concentration data will be analyzed using non-compartmental methods. Peak drug concentration (Cmax), time of maximum observed concentration (Tmax) and area under the plasma-concentration-time curve from

time 0 to 8 h (AUC_{0-8h}) of pexidartinib and its metabolite will be estimated on Days 1 and 15.

Key Efficacy Parameters:

Tumor response will be evaluated using Response Evaluation Criteria In Solid Tumors (RECIST) Version 1.1. Subjects will be classified into the best of the following tumor response categories: CR, PR, SD, progressive disease, or not evaluable. All efficacy variables will be presented in listings by subject. The number and percentage of subjects in each response category will be summarized along with the number and percentage of subjects with an objective response (CR or PR) and a DCR (CR or PR or SD). Exact binomial 95% confidence intervals (CIs; 2-sided) will be provided for each category response and the best ORR.

Key Pharmacodynamic Parameters:

Plasma PD variable: CSF-1 and adiponectin.

The PD variable concentration values will be listed by cohort. Summary tables of values at each time point will be created for the PD variable (CSF-1 and adiponectin), details of which will be added in the Statistical Analysis Plan (SAP).

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LIST OF ABBREVIATIONS

ABBREVIATION	DEFINITION
AE	adverse event
ALT	alanine aminotransferase
AML	acute myeloid leukemia
AST	aspartate aminotransferase
$AUC_{0\text{-}xh}$	area under the plasma-concentration-time curve from time zero to X hours (X denotes the number)
AUCinf	area under the plasma-concentration-time curve from time zero to infinity
CDISC	Clinical Data Interchange Standards Consortium
CHF	congestive heart failure
CI	confidence interval
Cmax	peak drug concentration
CR	complete response
CSF-1	colony-stimulating factor-1
CSF1R	receptor of colony-stimulating factor-1
CT	computed tomography
CXDX	Cycle X On Day X (X denotes the number)
CYP	cytochrome P450
DCR	disease control rate
DLT	dose-limiting toxicity
ECG	electrocardiogram
ECHO	echocardiogram
ECOG PS	Eastern Cooperative Oncology Group Scale of Performance Status
eCRF	electronic Case Report Form
EDC	Electronic Data Capture
EIU	exposure in utero
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GGT	gamma glutamyl transferase
GIST	gastrointestinal stromal tumor
GLP	Good Laboratory Practice
HCl	hydrochloride
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonisation
Ig	Immunoglobin
IL	interleukin
INR	International Normalized Ratio
IRB	Institutional Review Board
ITD	internal tandem duplications
LH	luteinizing hormone

ABBREVIATION	DEFINITION
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
MUGA	multi-gated acquisition
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Events
NYHA	New York Heart Association
ORR	objective response rate
OTC	over-the-counter
PD	pharmacodynamics
PK	pharmacokinetics
PGx	pharmacogenomics
PPI	proton pump inhibitors
PR	partial response
PVNS	pigmented villonodular synovitis
QTc	QT interval corrected for heart rate
QTcF	Fridericia corrected QT interval
RANK-L	receptor activator of nuclear factor kappa-B ligand
RECIST	Response Evaluation Criteria In Solid Tumors
RNA	ribonucleic acid
RP2D	recommended Phase 2 dose
SAE	serious adverse event
SAP	Statistical Analysis Plan
SAVER	Serious Adverse Event Report
SD	stable disease
SMC	Safety Monitoring Committee
SOC	System Organ Class
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment-emergent adverse event
TGCT	tenosynovial-giant cell tumor
Tmax	time of maximum observed concentration
TTR	time to response
ULN	upper limit of normal
US	United States

1. INTRODUCTION

1.1. Background

PLX3397 (pexidartinib) is a novel, orally active, small molecule inhibitor that targets Fms (receptor for colony-stimulating factor-1 [CSF1R], also known as macrophage colony-stimulating factor, as well as the newly described ligand interleukin [IL]-34), Kit (the receptor for stem cell factor), and oncogenic Flt3 (the receptor for Flt3 ligand), but remains highly selective versus other kinases. The potent inhibition of these 3 kinases can be exploited to attack tumors via multiple mechanisms. For example, somatic activation of Kit and Flt3 has been well-documented in multiple cancers. Beyond the direct dependence of tumors on these oncogenic drivers, Fms and Kit are regulators of macrophages, osteoclasts, microglia, and mast cells that are key components of various tumor microenvironments that support cancer growth, survival, invasion, and metastasis. Therefore, pexidartinib has the potential to antagonize cancer by the following mechanisms:

- Directly inhibiting oncogenic drivers such as oncogenic Kit and Flt3 mutant proteins[1, 2]
- Inhibiting paracrine loops between stromal cells and tumors[3, 4]
- Blocking migration and angiogenesis[5, 6, 7]
- Reprogramming tumor immune microenvironment
- Disrupting osteolytic metastases[8, 9]

An important role for tumor infiltrating macrophages in tumor progression has pointed to Fms as a key target in multiple tumor types.[5] The pro-tumorigenic role of colony-stimulating factor-1 (CSF-1) and Fms is strongly supported by a wealth of studies demonstrating that CSF-1 levels predict a poor outcome in a variety of oncology indications, including breast, ovarian, non-small cell lung, and colorectal cancers.

Treatment of breast cancer xenografts with antisense antibodies or small interfering ribonucleic acid (RNA) to CSF-1 suppresses tumor growth. The mechanism for this inhibition relates in part to a paracrine loop that links CSF-1-secreting tumor cells with epidermal growth factor-secreting macrophages.[3] Furthermore, a growing body of literature has now linked macrophages to angiogenesis.[5] It has now been recognized that various chemotherapies or radiotherapy may cause tumor cells to hypersecrete CSF-1 and/or IL-34, resulting in accumulation of tumor-associated macrophages.[10] In animal models, combination chemotherapy with pexidartinib results in substantially enhanced efficacy. Pexidartinib causes modulation of tumor-associated macrophages and/or myeloid-derived suppressor cells that may potentially be beneficial in enhancing antitumor responses when used in combination with immune checkpoint inhibitors.

The pro-tumorigenic and chemotherapy-resistance role of tumor-associated macrophages is not limited to breast cancer and may include additional tumor types such as melanoma, prostate cancer, and pancreatic cancer, among others. Accordingly, pexidartinib has

demonstrated therapeutic efficacy as a single agent and in combination with chemotherapy or radiation in nonclinical models of pancreatic[11] and prostate cancer.[12]

The efficacy of osteoclast antagonists such as bisphosphonates in preventing bone fractures and pain resulting from osteolytic metastases has been recognized for some time.[13] Osteoclasts require the parallel activation of the receptor activator of nuclear factor kappa-B ligand (RANK-L) and Fms pathways for activity and survival. Recently, RANK-L antagonists have demonstrated efficacy to prevent bone destruction in nonclinical models, and denosumab is now a United States (US) Food and Drug Administration-approved RANK-L-targeting antibody.[9] As a potent inhibitor of Fms, the anti-osteoclast effects of pexidartinib that are seen in vitro and in vivo provide an alternative mechanism to block bone destruction and consequent pain.

Tumor responses in patients with acute myeloid leukemia (AML) using inhibitors of mutant Flt3 have been reported, although none of these inhibitors have been approved to treat AML.[2] Pexidartinib preferentially inhibits oncogenic Flt3 internal tandem duplications (ITD) versus the wild type protein, which may translate into a higher therapeutic index than currently approved therapies. Tumor control due to blockade of Kit mutations has been validated through the established efficacy of imatinib and sunitinib (both with inhibitory activity against selected Kit-mutated tumors) in gastrointestinal stromal tumors (GIST).[1]

1.2. Intended Use Under Investigation

Pexidartinib will be evaluated in subjects with advanced solid tumors.

1.3. Nonclinical Studies

When screened in vitro against a broad panel of 230 kinases, pexidartinib shows potent and selective inhibition against its intended targets: CSF1R, Kit, and activated Flt3. Pexidartinib also blocks osteoclast differentiation and cell growth of CSF-1-dependent cell lines. Pexidartinib has shown the ability to block CSF1R activity in a variety of in vivo models. Pexidartinib shows dose-dependent inhibition of splenomegaly in an engineered CSF1R-dependent mouse model. Additionally, pexidartinib shows a potent inhibitor of the proliferation of Flt3-ITD-dependent models or Kit-dependent models.

Additional detailed information regarding the nonclinical pharmacology and toxicology of pexidartinib can be found in the Investigator's Brochure (IB).

1.4. Clinical Studies

Pexidartinib has been evaluated in multiple clinical studies (Table 1.1); as of 31 Jul 2015, the safety and pharmacodynamics (PD) effects of pexidartinib has been evaluated in 10 clinical studies, of which 3 have been completed: study PLX108-03 in patients with relapsed or refractory Hodgkin's lymphoma, study PLX108-04 in recurrent glioblastoma multiforme (GBM), and study PLX108-06 in patients with advanced metastatic prostate cancer. In addition, single-dose studies PLX108-11 and PLX3397-A-U114 were completed in healthy subjects. Seven ongoing studies are evaluating pexidartinib in patients with advanced incurable solid tumors focusing on pigmented villonodular synovitis (PVNS) (PLX108-01 and PLX108-10), relapsed or refractory AML

(PLX108-05), combination therapy in advanced incurable solid tumors (PLX108-07, with paclitaxel; PLX108-14, with pembrolizumab), in newly diagnosed glioblastoma multiforme (GBM) (PLX108-08, with temozolomide and radiation), and in BRAF-mutated metastatic melanoma (PLX108-09, with vemurafenib).

Table 1.1: Summary of Clinical Studies with Pexidartinib as of 31 Jul 2015

Study Number/ Start Date[a]/Status/ Country	**Dosing Regimen**	**Study Population**	**Enrollment[b]**
PLX108-01/ 01 Oct 2009/ Ongoing/ US	Pexidartinib 200 mg QD (Starting dose); RP2D: 1000 mg/d (administered as BID)	Adults with advanced, incurable, solid tumors; ongoing extension cohort focused on Pigmented Villonodular Synovitis (PVNS)	Planned: up to 50 patients in the dose escalation phase; 70 patients in 6 extension cohorts and up to 30 additional patients in a specific cohort Actual: 134
PLX108-03/ 02 Mar 2011/ Complete/ US	Pexidartinib, oral, capsule (100 mg per capsule) at 900 mg/d	Adults with relapsed or refractory Hodgkin's lymphoma	Planned: 30 Actual: 20
PLX108-04/ 13 Dec 2011/ Complete/ US	Pexidartinib, oral, BID capsule (100 mg or 200 mg per capsule) at 1000 mg/d	Patients with recurrent glioblastoma multiforme	Planned: 40 Actual: 38
PLX108-05/ 14 Nov 2011/ Ongoing/ US	Pexidartinib oral, BID, capsule The dose level of pexidartinib in Part 2 was determined to be 3000 mg/d administered BID	Adults with relapsed or refractory Flt3-ITD positive acute myeloid leukemia	Planned: 90 Actual: 90
PLX108-06/ 25 May 2012/ No active patients/ US	Pexidartinib oral, BID, capsule at 1000 mg/d	Patients with progressive CRPC, bone metastases and high CTC counts	Planned: 20 Actual: 6
PLX108-07/ 15 May 2012/ Ongoing/ US	Pexidartinib, oral, BID, capsule at 600 mg/d, 800 mg/d, 1000 mg/d, 1200 mg/d, and 1600 mg/d Paclitaxel, IV, once weekly, 80 mg/m^2	Patients with advanced, incurable solid tumor; ongoing extension cohort focused on relapsed or refractory ovarian cancer, primary peritoneal cancer, or fallopian tube cancer	Planned: 90 Actual: 54

Table 1.1 Summary of Clinical Studies with Pexidartinib as of 31 Jul 2015 (continued)

Study Number/ Start Date[a]/Status/ Country	Dosing Regimen	Study Population	Enrollment[b]
PLX108-08/ 18 Jul 2013/ Ongoing/ US	Phase 1b: pexidartinib, oral, BID, 800 mg/d or 1000 mg/d; 60 Gy of radiation therapy over approximately 6 weeks; temozolomide 75 mg/m^2 PO once daily for approx. 6 weeks; 4-week no treatment period; and, adjuvant temozolomide 150 mg/m^2 once daily on Days 1-5 of each 28-day cycle Phase 2: RP2D from Phase 1b	Newly diagnosed glioblastoma	Planned: 79 Actual: 65
PLX108-09/ 23 Oct 2013/ Complete/ US, France, Germany	Dose Escalation Phase: pexidartinib 800 mg/d and vemurafenib 720 mg oral, BID; pexidartinib 800 mg/d and vemurafenib 960 mg, oral BID; pexidartinib 1000 mg/d and vemurafenib 960 mg, oral BID Extension cohort: RP2D (BID)	V600-mutated BRAF Unresectable or Metastatic Melanoma	Planned: 90 Actual: 13
PLX108-10/ 08 Apr 2015/ Ongoing/ US, Canada, Denmark, France, Germany, Hungary, Italy, Netherlands, Poland, United Kingdom, Spain, and Australia	Double blind phase: pexidartinib 1000 mg/d (400 mg am and 600 mg pm) or placebo for first 2 weeks and 800 mg/d (400 mg BID) or placebo for 22 weeks. Extension cohort: Open label pexidartinib at maximum starting dose of 400 mg BID.	PVNS/giant cell tumor of the tendon sheath (GCT-TS), also known as tenosynovial giant cell tumors (localized and diffuse types)	Planned: 126 Actual: 5

Table 1.1 Summary of Clinical Studies with Pexidartinib as of 31 Jul 2015 (continued)

Study Number/ Start Date[a]/Status/ Country	Dosing Regimen	Study Population	Enrollment[b]
PLX108-14/ 06 Jul 2015/ Ongoing/ US	Dose-escalation Phase (Part 1): Pembrolizumab 200 mg IV every 3 weeks in combination with a starting dose of pexidartinib at 600 mg/d, with sequential escalations to 800 and 1000 mg/d. Expansion Phase (Part 2): Pembrolizumab 200 mg IV every 3 weeks in combination with oral pexidartinib administered as a split dose at the RP2D of pexidartinib.	Dose-escalation Phase: Advanced solid tumors, all comers Expansion Phase: The following tumor types: Melanoma (treatment-naïve) Melanoma (primary progressive) Melanoma (secondary progressive) Non-small-cell lung cancer (salvage, all comers) Ovarian cancer Triple-negative breast cancer Squamous cell cancer of the head and neck Bladder cancer Pancreatic ductal adenocarcinoma Gastric cancer Gastrointestinal stromal tumor Leiomyosarcoma Cholangiocarcinoma	Dose-escalation Phase: Up to 24; Expansion Phase: Up to 475 with 28 to 48 subjects per tumor type Actual: 3
PLX108-11/ 03 Jul 2014/ Complete/ US	Subjects randomized to receive treatments in 1 of 3 sequences of ABC, BCA, or CAB: Treatment A: 600-mg single dose of pexidartinib under fasted conditions; Treatment B: 600-mg single dose of pexidartinib under fed conditions (within 30 minutes after high-fat breakfast); Treatment C: 40 mg esomeprazole administered QD for 4 days, followed by 40 mg esomeprazole administered 2 h prior to a 600-mg single dose of pexidartinib under fasted conditions.	Healthy subjects	Planned: 27 Actual: 27

Table 1.1 Summary of Clinical Studies with Pexidartinib as of 31 Jul 2015 (continued)

Study Number/ Start Date[a]/Status/ Country	Dosing Regimen	Study Population	Enrollment[b]
PLX3397-A-U114/ 20 Nov 2014/ Complete/ US	Treatment A: pexidartinib 400 mg (J-3397-AE) Fasting Treatment B: Single dose pexidartinib 400 mg (J-3397-AF) Fasting Treatment C: Single dose pexidartinib 400 mg (J-3397-AF) Fed	Healthy subjects	Planned: 30 Actual: 30

Source: Table 23, DSUR, 2015 Versions 4.0 and DSUR addendum (Version 4.1).

BID = twice daily; CRPC = Castration-resistant prostate cancer; CTC = Circulating Tumour Cell; h = hours; IV = intravenous; QD = once daily; RP2D = recommended phase 2 dose; US = United States.

a Start date is the first visit for the first patient.

b Accrual is based on the total number of patients enrolled as of 31 Jul 2015.

No safety signals in vital signs, physical examinations, or electrocardiograms (ECGs) (including careful evaluation of potential ECG QT prolongation) have been identified. At doses of > 1000 mg/d, transient and reversible increases in alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) have been observed in approximately half of the patients. Similar increases in ALT and AST were seen in the 13-week rat study, but not in the dog study. Among solid tumor patients, the most common adverse events (AEs) (occurring in ≥ 20% of all patients treated with pexidartinib) observed have been fatigue, nausea, decreased appetite, hair color change (depigmentation), vomiting, diarrhea, headache, and anemia. In the AML study, the most common AEs reported have been diarrhea, nausea, fatigue, febrile neutropenia, vomiting, decreased appetite, anemia, cough, hypokalemia, and increases in AST.

Administration of single doses of 600 mg pexidartinib with a high fat meal resulted in increased peak drug concentration (Cmax) by 53% and AUC_{0-24} by 95% compared with the fasted state in healthy subjects (PLX108-11). Maximum plasma concentrations were obtained at a median Tmax of 4 hours (h) postdose, approximately 1 h later than observed in the fasted state. Mean half-life values were comparable, 26 and 30 h, following administration of 600 mg pexidartinib in the fed and fasted states, respectively.

Coadministration of pexidartinib with esomeprazole resulted in decreased exposure of pexidartinib as the mean Cmax and AUC_{0-24} for pexidartinib were 40% and 38%, respectively; lower when compared with administration of pexidartinib alone, all in the fasted state (PLX108-11).

Details on the clinical experience with pexidartinib can be found in the IB.

1.4.1. PLX108-01: US Phase 1 Study

PLX108-01 is evaluating patients with advanced, incurable, solid tumors in which the target kinases are linked to disease pathophysiology. This study is being conducted in 2 parts: an initial dose-escalation part to identify a recommended Phase 2 dose (RP2D), and an extension part to obtain preliminary efficacy data in patients with selected tumor types. The dose-escalation part of the study has been completed and 1000 mg/d, administered as a twice daily (BID) regimen, was selected as the maximum tolerated dose (MTD) and RP2D for further evaluation in the extension cohorts.

Dose-escalation Part

Forty-one patients enrolled in 7 dose-escalation cohorts received study drug, including 3, 6, 6, 6, 7, 6, and 7 patients in Cohorts 1 (200 mg once daily [QD]), 2 (300 mg QD), 3 (400 mg QD), 4 (600 mg QD), 5 (900 mg/d QD or BID), 6 (1200 mg/d BID), and 7 (1000 mg/d BID). Doses from 200 mg through 900 mg/d were administered as QD, whereas 1000 and 1200 mg doses were administered as BID. The 1000 mg/d dose, administered as a BID regimen, was selected as the MTD and RP2D.

Overall, reasons for study discontinuation were disease progression (29 [70.7%] patients), investigator decision (5 [12.2%] patients), AE (4 [9.8%] patients), patient decision (2 [4.9%] patients), and protocol violation (1 [2.4%] patient). The majority of patients completed at least 1 cycle of treatment; reasons for discontinuation prior to completion of Cycle 1 were disease progression (1 patient each in Cohorts 3, 5, and 7), investigator decision (1 patient each in Cohorts 2, 4, and 5), AE (1 patient each in Cohorts 4, 6, and 7), and protocol violation (1 patient in Cohort 5).

Patients enrolled in the dose-escalation phase had 18 different categories of primary tumor types at baseline, with primary tumor types reported by > 1 patient including rectal or colorectal (6 patients), colon and leiomyosarcoma (4 patients each), breast, ovarian, prostate, and unknown primary origin (3 patients each), and pancreatic, non-small cell lung cancer, bone, and endometrial (2 patients each). A higher proportion of female patients (61.0%) than male patients (39.0%) enrolled in the study. The majority of patients were White (97.6%) and not Hispanic or Latino (92.7%). The mean age overall was 58.3 years with a range of 22 to 79 years. All patients had an Eastern Cooperative Oncology Group Scale of Performance Status (ECOG PS) of 0 or 1 at screening, as required per protocol.

Forty (97.6%) patients experienced ≥ 1 AE during the dose-escalation phase; 1 patient in Cohort 5 (900 mg/d) did not experience AEs. The most common AEs (> 10% overall incidence), irrespective of relationship to study drug, were nausea (46.3%), decreased appetite (43.9%), anemia and fatigue (41.5% each), vomiting (39.0%), dehydration (24.4%), diarrhea (22.0%), hair color changes (19.5%), back pain, dizziness, dyspnea, and pyrexia (17.1% each), upper abdominal pain, constipation, and headache (14.6% each), and AST increased, dysgeusia, and musculoskeletal pain (12.2% each).

Six (14.6%) patients experienced a total of 9 dose-limiting toxicity (DLT) AEs, including 1 patient in Cohort 2 (300 mg QD, [International Normalized Ratio {INR} increased and hematuria]), 2 patients in Cohort 4 (600 mg QD, [lymphocyte count decreased] and [hyponatremia]), 2 patients in Cohort 6 (1200 mg/d BID, [AST increased] and [anemia,

neutropenia, and syncope]), and 1 patient in Cohort 7 (1000 mg/d BID, [AST increased]). All but two of the DLT AEs were considered possibly or probably related to study drug; hematuria (300 mg QD, Cohort 2) and hyponatremia (Cohort 4, 600 mg QD) were considered unlikely related to study drug. The DLT dose was determined to be reached at 1200 mg/d (Cohort 6), resulting in an MTD and RP2D of 1000 mg/d (Cohort 7).

Among the 35 patients in the dose-escalation phase of Study PLX108-01 with evaluable efficacy information, no patient achieved a complete response (CR), 1 (2.9%) patient achieved a partial response (PR), 8 (22.9%) patients achieved stable disease (SD), 22 (62.9%) patients had progressive disease, and 4 (11.4%) patients were not evaluable for the best tumor response. A confirmed PR was achieved by one patient, a 40 year old female with mucoepidermoid carcinoma of the salivary gland in Cohort 7 (1000 mg/d, MTD). Stable disease was reported in 1 patient each (range: 16.7% to 20.0%) in Cohort 2 (300 mg QD), 6 (1200 mg/d), and 7 (1000 mg/d, MTD); 2 patients (40.0%) in Cohort 4 (600 mg QD); and 3 patients (50.0%) in Cohort 5 (900 mg/d). The proportion of patients with SD was not dose related in the dose-escalation phase of the study.

In each dose-escalation cohort, patients received pexidartinib on the morning of Cycle 1. On Day 1 (C1D1) and on Day 15 (C1D15), patients underwent pharmacokinetic (PK) sampling. For QD dosing, PK samples were collected prior to dosing and at 0.5, 1, 2, 4, 8, and 24 h following dosing. For BID dosing, PK samples were obtained predose in the morning and 1, 2, 4, 7 h postdose on C1D1 and C1D15. The second dose was then administered and a 1-h post second-dose sample (8 h after the first dose) and a 24-h post first-dose sample was obtained. In the extension cohort, PK samples were obtained predose and at 1, 2, 4, and 6 h postdose on the morning of C1D15.

For the dose range of 200 to 1200 mg/d, the median Tmax on Day 1 was 2.0 h and Cmax values ranged from 1350 to 5250 ng/mL; on Day 15, the median Tmax was 2.0 h and Cmax values ranged from 2030 to 9220 ng/mL. Not only was Tmax reached quickly after dosing, but it was also relatively consistent across cohorts with median values ranging from 0.975 to 2.03 h. Similar to Cmax, mean AUC_{0-24} estimates generally increased with the increasing dose; mean AUC_{0-24} estimates ranged from 25550 ng•h/mL in the 200 mg QD cohort to 147000 ng•h/mL in the 1200 mg/d cohort.

A comparison of concentration versus time data for individual patients between Day 1 and Day 15 suggests some potential for pexidartinib to accumulate after 15 days of dosing. Thus, the mean PK Cmax and AUC_{0-6} values were higher for Day 15 than for Day 1. The accumulation ratio provides an assessment of how much a drug accumulates during a dosing regimen between when dosing starts and at steady state. The accumulation ratio for mean AUC during 1 dosing interval for Day 1 compared with Day 15 was approximately 2.

Reductions in the CD14+/CD16+ cell populations have also been observed in most patients treated to date. Serum CSF-1 levels have increased in most patients after initiation of pexidartinib dosing, as would be anticipated from Fms inhibition, resulting in reduced clearance of the ligand. Importantly, higher plasma pexidartinib concentrations are associated with higher elevations of CSF-1, supporting a concentration-dependent pathway inhibition. Urinary N-telopeptide concentrations showed a concentration-dependent decrease from baseline, consistent with osteoclast inhibition.

Clinically relevant increases in adiponectin were also observed, with 2- to 3- fold increases from baseline generally observed in patients treated at dose levels of 900 mg/d and higher.

Dose Extension Part

The cohort-extension part of the study is ongoing and final analysis of efficacy data has not been completed. As of 31 Jul 2015, 66 patients have been enrolled into the extension cohorts: 1) mucoepidermoid carcinoma of the salivary gland, 2) tenosynovial-giant cell tumor (TGCT), 3) GIST, 4) anaplastic thyroid carcinoma, 5) solid tumors with documented malignant pleural or peritoneal effusions, and 6) miscellaneous tumor types. The current focus of the extension-cohort is to evaluate pexidartinib in the treatment of TGCT. As of 31 Dec 2014, 31 patients have been enrolled in the TGCT cohort.

An analysis was performed using data as of 31 Dec 2014 (data cut performed on 27 Feb 2015) for 31 patients with TGCT treated with pexidartinib at 1000 mg/d given as a split dose. Median exposure for this cohort was 254 days, and the longest treatment duration was 748 days.

Of the 31 intent-to-treat (ITT) patients, 29 were evaluable (i.e., had a baseline and at least one post-baseline MRI) for response by Response Evaluation Criteria In Solid Tumors (RECIST) 1.1 per local reading, and 14 had a PR, for an objective response rate (ORR) of 45% (95% CI: 27–64%) and 48% (95% CI: 29–67%) for the ITT and evaluable patients, respectively. An additional 13 patients had SD at the time of the analysis for a disease control rate (DCR = PR + SD) of 87% (95% CI: 70–96%) and 93% (CI: 77 –99%) for the ITT and evaluable patients, respectively.

Additional detailed information regarding the clinical pharmacology and toxicology of pexidartinib can be found in the IB.

1.5. Study Rationale

As this is the first time pexidartinib will be studied in an Asian country, the dose-escalation part of the study will confirm the safety and tolerability of 1000 mg/d in subjects with advanced solid tumors. The dose escalation will start from 600 mg/d and will be escalated to 1000 mg/d as the highest dose level for 2 weeks and then reduced to 800 mg/d continuously.

Selection of the pexidartinib dose of 1000 mg/d as the highest dose and the split-dose administration schedule is based on data from patients with solid tumors, including the cohort of patients with TGCT who received pexidartinib in Study PLX108-01, a Phase 1 study. In the dose-escalation part of that study, 2 subjects receiving 1200 mg/d, administered as a split dose, experienced DLTs of anemia, neutropenia, and syncope in 1 patient and elevated AST in the other. For this reason, 1000 mg/d given as a split dose was selected as the MTD and the RP2D for TGCT.

Data from the TGCT cohort in Study PLX108-01, a Phase 1 study, suggests that some patients may require dose modification. Therefore, the dose regimen has been changed to 1000 mg/d as the initial dose, followed by 800 mg/d after 2 weeks.

For detailed information regarding the Study PLX108-01 study, refer to the IB.

This study will evaluate the safety, tolerability, and PK profile in Asian subjects with advanced solid tumors.

Extension part of the study will allow subjects who received pexidartinib as part of a clinical study to continue treatment. The benefits of transitioning subjects into extension part are to:

- Reduce complexity of Follow-up, allowing subjects to continue receiving the study drug and facilitate their participation.
- Continue to monitor and collect long-term safety data.

1.6. Risks and Benefits for Study Subjects

The safety of pexidartinib has been evaluated in subjects with a range of tumor types, including solid tumors, hematologic malignancy, and in combination with chemotherapeutic agents. The selection of 1000 mg/d as the initial dose to be evaluated in the several studies was based upon the safety data from Study PLX108-01 and the safety of 1000 mg/d was further evaluated in several clinical studies.

In the Good Laboratory Practice (GLP) repeat-dose toxicology studies consisting of up to 13 weeks of pexidartinib dosing, test article-related AEs were noted in testes (testicular-spermatogonia reduction), ovaries (ovarian follicular degeneration), liver, bone and bone marrow, hematology, and lymphoid changes; these changes are consistent with the pharmacological mechanism of action of pexidartinib. All test article-related findings were partially or fully reversible. Potential dose-related changes in bone marrow function can be monitored by peripheral blood cell count and differential counts. Because of the effects on reproductive organs, subjects will be monitored for changes in luteinizing hormone (LH), follicle-stimulating hormone (FSH), and other sex-specific hormone levels.

Effects on embryo fetal development have been observed in both rat and rabbit toxicology studies. Subjects in the study will be required to use adequate birth control during the study and for 90 days after the last dose of study drug administered.

Findings in the nonclinical canine safety pharmacology study suggest that pexidartinib may have a negative inotropic effect. Subjects will be monitored for changes in ejection fraction with cardiac echocardiograms (ECHOs).

In the clinical evaluation to date, among solid tumor patients, the most common adverse events (AEs) (occurring in $\geq$ 20% of all patients treated with pexidartinib) observed have been fatigue, nausea, decreased appetite, hair color change (depigmentation), vomiting, diarrhea, headache, and anemia. In the AML study, the most common AEs reported have been diarrhea, nausea, fatigue, febrile neutropenia, vomiting, decreased appetite, anemia, cough, hypokalemia, and increases in AST. In some instances, the increase in liver enzymes may require dose hold or modification. Dosing modification guidance is included within the protocol for AE monitoring (Table 5.2). Liver function (clinical chemistry), renal function (clinical chemistry), and heart electrophysiology (QT interval corrected for heart rate [QTc] evaluation) will be monitored during this study.

Based on the treatment-emergent adverse event (TEAE) reports of increased INR observed in patients receiving concomitant warfarin, careful monitoring is required during treatment with pexidartinib. Warfarin doses should be adjusted if an increase in INR is noted.

Pexidartinib is a novel, orally active, small molecule inhibitor that targets CSF1R, Kit, and oncogenic Flt3, but remains highly selective versus other kinases. The potent inhibition of these 3 kinases can be exploited to attack tumors via multiple mechanisms. Pexidartinib has shown a potent inhibitor of the proliferation of these target-dependent models.

In summary, given the acceptable safety profile of the pexidartinib at the selected dose levels, and nonclinical data and Phase 1 data in patients with TGCT, the potential for a positive benefit/risk profile is assumed in the Phase 1 study.

1.6.1. Updated Risk Information

During the conduct of this study, important safety information received from one ongoing Daiichi Sankyo phase III pexidartinib study (ENLIVEN) on indication of PVNS or giant cell tumor of the tendon sheath with daily dose of 1000 mg/day for the first two weeks then 800 mg/day. In the ongoing ENLIVEN study, two Serious Adverse Events (SAEs) of hyperbilirubinemia concurrent with transaminase increase were identified recently. There were an estimated 80 patients who had been exposed to pexidartinib in ENLIVEN study. The initial case, a 75 year old woman with few risk factors, experienced hyperbilirubinemia for 2.5 months (ongoing), requiring study drug discontinuation, hospitalization and two liver dialysis procedures. A liver biopsy showed cholestasis and ductopenia. The second case, a 52 year old male with few risk factors, had grade 4 liver enzyme increase concurrent with hyperbilirubinemia, which resolved on study drug discontinuation without further measures. Both cases were not re-challenged with the study drug.

Five cases of this pattern of liver dysfunction have been observed in other pexidartinib trials, both in monotherapy and combination therapy. In total there are now 7 cholestatic/mixed type of liver dysfunction cases reported among approximately 550 subjects. Among the five cases including one case from in this PL3397-A-A103 study, prolonged hyperbilirubinemia (> 8 months, ongoing) occurred in one case and two other cases took 2-3 months to resolve. All cases occurred between 14 and 57 days of the start of pexidartinib treatment, suggesting a higher risk within the first 8 weeks of treatment. Three of the 7 cases had liver biopsy showing cholestasis and ductopenia.

In response to the updated safety information, the study safety monitoring committee (SMC) meeting was held to review relevant data of this study. The SMC recommended safety measures that changed the conduct of this study to enhance the protection of subjects. The following actions have been provided in study memos issued on 07 Oct 2016 and 14 Oct 2016:

- Enrollment of any new non-malignant tumor including TGCT patients was stopped.

- For non-malignant tumor including TGCT patients in screening, the screening should be stopped and discuss with patients about alternative treatment of their disease.
- For all patients with ongoing pexidartinib treatment, the patient of the new safety findings should be informed at their next visit/contact. After the consultation, if it is deemed to be in their best interest to continue treatment, the patient should be re-consented. If the updated informed consent form (ICF) is not available, document this discussion in the patient's record and collect the signed updated ICF when available.
- Enrolment of patients with malignant tumor is allowed. The enrolment based on study inclusion/exclusion criteria would be continued and the patient of the new safety findings should be informed. If the updated ICF is not available, document this discussion in the patient's record and collect the signed updated ICF when available.
- As the cases of severe cholestatic liver dysfunction were observed in cycles 1 and 2 of the study drug, Sponsor request following measures to be taken immediately to make sure patient safety is well-monitored.
    - Include Gamma glutamyl transferase (GGT) test in liver function test panel (Table 9.1 of the protocol)
    - Increase liver function test frequency to weekly from Cycle 1 Day 1 to Cycle 3 Day 15 and then biweekly until Cycle 5 Day 1

Updated hepatic safety risk information as of December 2017; please consult the IB for more information: Hepatotoxicity is an important adverse drug reaction. Elevations of liver transaminases and bilirubin have been observed in studies with pexidartinib, together with cases of drug induced cholestasis. Cases of cholestasis have been observed in the first 8 weeks, have generally resolved with treatment discontinuation, but in some cases have been severe, with a protracted course requiring liver dialysis and, in 1 case, transplantation. Hepatotoxicity may be fatal. One fatal case with ongoing cholestatic liver injury at the time of death has been reported. Monitor patients closely as defined in the protocol. Protocol defined dose reductions and discontinuations of pexidartinib, increased frequency of laboratory monitoring, and reporting of findings should be followed (refer to Section 5.7). In addition, rechallenge with pexidartinib should not be attempted without prior discussion with the Sponsor's Medical Monitor.

2. STUDY OBJECTIVES AND HYPOTHESIS

2.1. Study Objectives

2.1.1. Primary Objectives

- To assess the safety and tolerability of pexidartinib in Asian subjects with advanced solid tumors
- To determine the RP2D of pexidartinib in Asian subjects with advanced solid tumors

2.1.2. Secondary Objectives

- To assess the PK profile of pexidartinib and its metabolite
- To assess the PD effect of pexidartinib on CSF-1 and adiponectin level in plasma
- To evaluate the preliminary efficacy of pexidartinib
- To evaluate ORR rate (the sum of CR rate and PR rate)
- To evaluate DCR (the sum of CR rate, PR rate, and SD rate)
- To evaluate response duration
- To evaluate duration of SD
- To evaluate time to response (TTR)
- To evaluate percentage of change in target lesion(s)

2.1.3. Exploratory Objectives

- To explore the effect of UGT1A4 genotype on pexidartinib PK
- To explore any possible correlation of genomics to pexidartinib safety

2.2. Study Hypothesis

Pexidartinib will be safe and well-tolerated and exhibits acceptable PK properties in Asian subjects with advanced solid tumors. Subjects who have not progressed while receiving pexidartinib will continue to tolerate and to benefit from longer administration of the study drug in the extension part. See Section 11.6 for sample size determination.

3. STUDY DESIGN

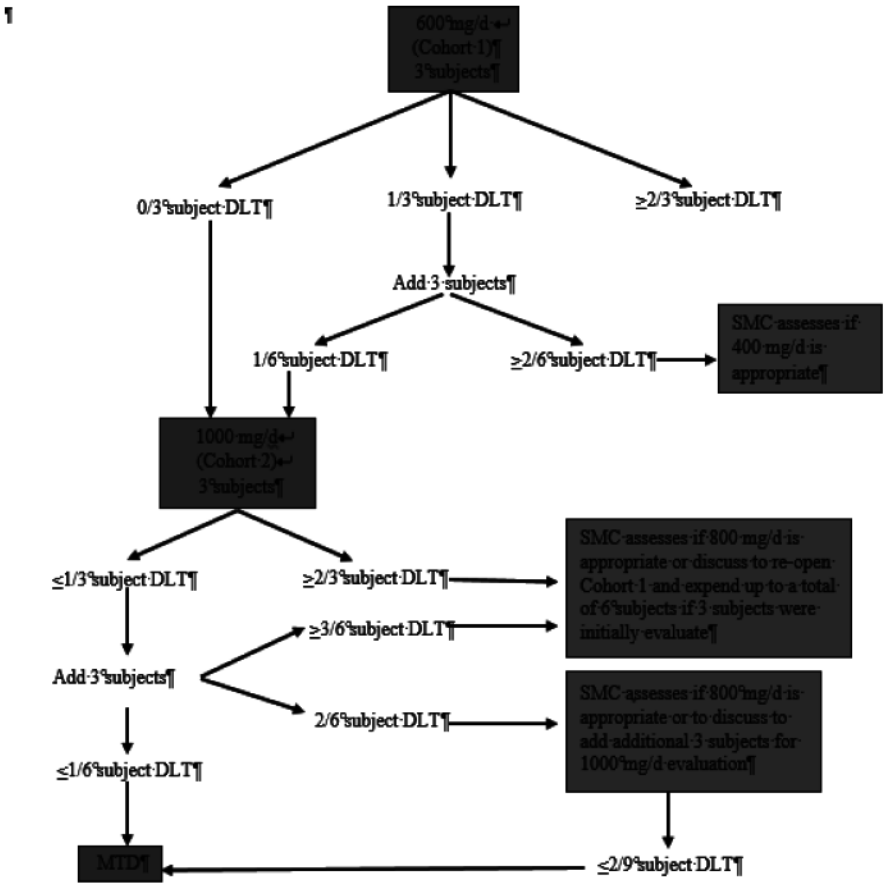
3.1. Overall Design

This is a Phase 1, non-randomized, open-label, multiple-dose study of pexidartinib in Asian subjects with advanced solid tumors. The study will be conducted in a dose-escalation 3+3 design. This study comprises 2 dose levels (Cohort 1 and Cohort 2) to assess the safety and tolerability, RP2D, PK and PD, and preliminary antitumor activity of pexidartinib.

- Cohort 1: 600 mg/d (200 mg in the morning, 400 mg in the evening)
- Cohort 2: 1000 mg/d (400 mg in the morning and 600 mg in the evening) for the first 2 weeks. Thereafter, the dose will be reduced to 800 mg/d (400 mg in the morning and 400 mg in the evening).

For the detailed dose level escalation method and the definition of DLT, refer to Section 5.6 and Figure 3.1. Dose reductions and interruptions for toxicity will be permitted according to pre-specified guidelines (Section 5.7).

Figure 3.1: Study Schematic



DLT = dose-limiting toxicity; MTD = maximum tolerated dose; SMC = Safety Monitoring Committee.

Pexidartinib will be administered orally in capsule form. Pexidartinib will be supplied in 200 mg capsules and will be taken BID approximately 12 h apart in the morning and evening. Doses will be taken in the fasting state (no food for 1 h before and 2 h after dosing, with a low-fat snack if needed). Each cycle of treatment will be 28 days in duration. Subjects will continue study visit in dose escalation part till the cut-off date (The cut-off is defined as the date after all subjects have either discontinued the study or completed at least 4 cycles. Subjects who are still ongoing in the study after the cut-off date and who are responding or stable after pexidartinib during the dose escalation part will enter extension part to receive extended treatment of pexidartinib. The cycle of treatment will be continued until disease progression, unacceptable toxicity, or consent withdrawal.

3.2. Discussion of Study Design

This study will evaluate the safety, tolerability, and PK profile in Asian subjects with advanced solid tumors as currently not much safety data are available in these subjects. Pexidartinib capsules (200 mg strength) will be administered.

The dose-escalation plan is selected on the basis of data from Study PLX108-01, a US Phase 1, open-label, 2-part study of single agent pexidartinib in subjects with advanced, incurable, solid tumors (Part 1) and in subjects with selected tumors (Part 2). The initial dose-escalation part of the study (Part 1) studied total daily oral doses from 200 mg through 1200 mg. Two subjects receiving 1200 mg/d, administered as a split dose, experienced DLT toxicities: anemia, neutropenia, and syncope in 1 subject and elevated AST in the other. One of 7 subjects receiving 1000 mg/d, administered as a split dose, experienced a DLT of AST increased. Thus, a RP2D of 1000 mg/d as a split dose was administered in the extension cohorts (Part 2) of this single agent study. An interim analysis from the extension cohort with the longest duration of treatment (median duration of 219 days, n = 17 subjects) showed that approximately half of the subjects required a dose reduction to at least 800 mg/d as a split dose within the first 2 cycles. Biomarker data has suggested that doses at or below 400 mg/d are less likely to have PD activity. Thus, in consideration of data from single agent pexidartinib, 600 mg/d as a split dose is selected as the initial dose with an allowance for de-escalation to 400 mg/d as a split dose.

3.3. Duration of the Study

The study duration is expected to last approximately 4 years from the time the first subject is enrolled until the last subject is off the study (including Follow-up visit).

3.4. Duration of Subject Participation

The number of treatment cycles is not fixed in this study. Subjects who derive clinical benefit from treatment in the absence of subject's consent withdrawal, disease progression, or unacceptable toxicity may continue another cycle of treatment at the investigator's discretion.

4. STUDY POPULATION

Subjects must sign and date the ICF provided by the study site before any study-specific qualification procedures are conducted.

4.1. Inclusion Criteria

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

1. Age should be ≥ 20 years.
2. Subjects must have a pathologically documented solid tumor that has relapsed from, or is refractory to standard treatment, or for which no standard treatment is available.
3. Women of childbearing potential must have a negative serum pregnancy test within the 14-day period prior to treatment allocation.
4. Men and women of childbearing potential are permitted in the study as long as they consent to avoid getting their partner pregnant or becoming pregnant themselves, respectively, by using a highly effective contraception method, as described below, throughout the study and for up to 90 days after completion. Highly effective methods of contraception include: hormonal methods associated with inhibition of ovulation, intra-uterine device, surgical sterilization (including partner's vasectomy), or sexual abstinence.
5. Women of non-childbearing potential may be included if they are either surgically sterile or have been postmenopausal for ≥ 1 year. Women who have documentation of at least 12 months of spontaneous amenorrhea and have an FSH level > 40 mIU/mL will be considered postmenopausal.
6. All associated toxicities from previous cancer therapy must have been resolved (to ≤ Grade 1 or baseline) prior to administration of pexidartinib.
7. ECOG PS of 0 or 1.
8. Life expectancy ≥ 3 months, in the opinion of the investigator.
9. Adequate hematologic, hepatic, and renal function defined by:
   - Absolute neutrophil count ≥ 1.5×10^9/L
   - Platelet count ≥ 100×10^9/L
   - ALT or AST ≤ 1.5 × upper limit of normal (ULN) (if liver metastases are present or subjects with hepatocellular carcinoma, ≤ 3 × ULN)
   - Albumin ≥ 3 g/dL
   - Total bilirubin ≤ 1.5 × ULN
   - Hemoglobin > 9 g/dL
   - Serum creatinine ≤ 1.5 × ULN or calculated creatinine clearance > 60 mL/min using the Cockcroft-Gault formula
10. Adequate treatment washout period before registration defined as:

- Major surgery: ≥ 4 weeks (2 weeks for less invasive surgery, such as colostomy)
- Radiation therapy (eg, whole brain radiotherapy): ≥ 4 weeks (if palliative stereotactic radiation therapy, ≥ 2 weeks)
- Chemotherapy or immunotherapy (including targeted therapy with antibody or small molecule, retinoid therapy, and hormonal therapy): 4 weeks or 5 half-lives of the agent, whichever is shorter (if the regimen has contained nitrosoureas or mitomycin C, ≥ 6 weeks)
- Other investigational drug therapy: ≥ 4 weeks

11. Willingness and ability to provide written informed consent prior to any study-related procedures and to comply with all study requirements.

4.2. Exclusion Criteria

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

1. Refractory nausea and vomiting, malabsorption, external biliary shunt, or significant small bowel resection that would have precluded adequate absorption.
2. Presence of a medical or psychiatric condition that, in the opinion of the investigator, made the subject inappropriate for inclusion in this study.
3. Previous use of pexidartinib or any biologic treatment targeting CSF-1 or the CSF1R; previous use of oral tyrosine kinase inhibitors, eg, imatinib or nilotinib, is allowed.
4. Clinically active primary central nervous system tumors or brain metastasis, defined as untreated and symptomatic, or requiring therapy with steroids or anticonvulsants to control associated symptoms.
5. Active or chronic infection with hepatitis C or known positive hepatitis B surface antigen, or known active or chronic infection with human immunodeficiency virus.
6. Known active tuberculosis.
7. Women who are breastfeeding.
8. A screening Fridericia corrected QT interval (QTcF) ≥ 450 ms (men) or ≥ 470 ms (women).
9. A medical history or complications of clinically significant lung disease (eg, interstitial pneumonia, pneumonitis, pulmonary fibrosis, and severe radiation pneumonitis).
10. A history of symptomatic congestive heart failure ([CHF]; New York Heart Association [NYHA] Classes II to IV) or serious cardiac arrhythmia requiring treatment.
11. A history of myocardial infarction or unstable angina within 6 months before enrollment.
12. An uncontrolled infection requiring intravenous injection of antibiotics, antivirals, or antifungals.

5. STUDY TREATMENT

For details and handling of the study drug, refer to the IB and the manual for management of the study drug available in the Study Reference Manual.

The investigator must ensure that the study drug will be used only in accordance with the protocol.

5.1. Assigning Subjects to Treatments and Blinding

5.1.1. Treatment Groups

This study comprises 2 dose levels (Cohort 1 and Cohort 2) to assess the safety and tolerability, RP2D, PK and PD, and preliminary antitumor activity of pexidartinib.

- Cohort 1: 600 mg/d (200 mg in the morning, 400 mg in the evening)
- Cohort 2: 1000 mg/d (400 mg in the morning and 600 mg in the evening) for the first 2 weeks. Thereafter, the dose would be reduced to 800 mg/d (400 mg in the morning and 400 mg in the evening)

Pexidartinib will be administered orally in capsule form. Pexidartinib will be supplied in 200 mg capsules and will be taken BID approximately 12 h apart in the morning and evening. Doses will be taken in the fasting state (no food for 1 h before and 2 h after dosing, with a low-fat snack if needed). Each cycle of treatment will be 28 days in duration. The cycles of treatment will be continued until disease progression, unacceptable toxicity, or consent withdrawal.

Treatment duration of pexidartinib is presented in Section 3.3.

5.1.2. Method of Treatment Allocation

The study design has been described in Section 3.

5.1.3. Blinding

The study is open-label and no blinding will be performed.

5.1.4. Emergency Unblinding Procedure

Not applicable.

5.2. Study Drug

5.2.1. Description

Pexidartinib is a hydrochloride (HCl) salt with a white to off-white crystalline solid appearance. Pexidartinib HCl will be supplied as a 200 mg capsule formulation J-3397-AF (200 mg free base equivalent) for oral administration containing the following excipients: Poloxamer 407, mannitol, crospovidone, and magnesium stearate.

The investigator must ensure that the study drug will be used only in accordance with the protocol.

5.2.2. Labeling and Packaging

Pexidartinib will be supplied by the Sponsor. Pexidartinib capsules (200 mg strength) are manufactured, packaged, and labeled according to Good Manufacturing Practice and Good Clinical Practice (GCP). The packaging will be clearly labeled "For Clinical Study Use Only," and will show the display name of the study drug, the study drug manufacturing code, storage condition, and other required information in accordance with local regulations.

5.2.3. Preparation

Pexidartinib is an anticancer drug, and as with other potential toxic compounds, caution should be exercised when handling pexidartinib. Specific instructions on preparation and dispensation will be provided in the Study Pharmacy Manual.

5.2.4. Administration

Pexidartinib should be taken BID approximately 12 h apart. Each dose is to be taken with 8 ounces (approximately 240 mL) of water. Pexidartinib should be given in the fasting state (no food for 1 h before and 2 h after dosing, with a low-fat snack if needed). Each cycle of treatment will be 28 days in duration. The cycle of treatment will be continued until disease progression, unacceptable toxicity, or consent withdrawal.

When an odd number of capsules is to be taken in a day, the larger number of capsules should be taken as the evening dose. For example, 600 mg/d = 3 capsules (1 capsule in the morning, 2 capsules in the evening). When an even number of capsules is to be taken in a day, the morning and evening doses should be the same (eg, 800 mg/d = 4 capsules (2 capsules in the morning, 2 capsules in the evening) or 400 mg/d = 2 capsules (1 capsule in the morning, 1 capsule in the evening).

5.2.5. Storage

Drug supplies must be stored in a secure, limited access storage area at 20°C to 25°C, with excursion permitted to 15°C to 30°C. If storage conditions are not maintained per specified requirements, the Sponsor or contract research organization should be contacted.

5.2.6. Drug Accountability

When a drug shipment is received, the investigator or designee will check the amount and condition of the drug, check for appropriate local language in the label, drug expiration date, and sign the Receipt of Shipment Form provided.

In addition, the investigator or designee shall contact Sponsor as soon as possible if there is a problem with the shipment.

A Drug Accountability Record will be provided for the study drug. The record must be kept current and should contain the dates and quantities of study drug received; the subject's identification number and/or initials or supply number as applicable, for whom

the study drug was dispensed; the date and quantity of study drug dispensed and remaining, as well as the initials of the dispenser.

At the end of the study, or as directed, all unused study drug will be returned to a designee as instructed by the Sponsor. Study drug will be returned only after the study monitor has completed a final inventory to verify the quantity to be returned. The return of study drug must be documented and the documentation included in the shipment. At the end of the study, a final study drug reconciliation statement must be completed by the investigator or designee and provided to the Sponsor.

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

5.3. Control Treatment

Not applicable.

5.4. Dose-limiting Toxicities

A DLT is defined as any drug-related TEAE that occurs during the first 28 days of treatment in each subject that meets the following NCI-CTCAE Version 4.0 criteria:

- For hematological toxicity, a DLT is defined as follows:
  - Grade 4 anemia
  - Grade 4 neutropenia lasting > 7 days
  - Grade ≥ 3 febrile neutropenia
  - Grade 4 platelet count decreased
  - Grade ≥ 3 platelet count decrease lasting > 7 days or associated with bleeding
- For hepatic major organ toxicity, a DLT is defined as follows:
  - Grade 4 ALT or AST increased
  - ALT or AST ≥ 3 × ULN, if accompanied with ≥ 2 × ULN in total bilirubin
  - ALT or AST > 5 × ULN lasting > 14 days
- Non-hematological toxicity, a DLT is defined as follows:
  - Grade≥ 3 non-hematological, non-hepatic major organ toxicity
  - Inability to complete at least 75% of the prescribed dose of pexidartinib in the first cycle as a result of drug-related TEAE

The following TEAE is NOT considered a DLT:

- Grade 3 nausea, vomiting or diarrhea that has resolved within 7 days with optimal prophylaxis and/or treatment
- Grade 3 fatigue that has resolved to Grade < 2 within 7 days
- Grade ≥3 alkaline phosphatase that is related to underlying malignancy (eg, bone metastasis)
- Laboratory data abnormalities determined to be transient by the investigator or isolated laboratory findings not associated with signs or symptom
- Grade 3/4 lymphocyte count decrease

5.5. Recommended Phase 2 Dose

Each treatment cycle will be 28 days in duration. The MTD will be defined as the dose at which ≤ 1 of 6 subjects experienced a DLT during Cycle 1. The RP2D will be determined based on the MTD.

If DLT is observed in 2 of 6 subjects in Cohort 2, the Safety Monitoring Committee (SMC) will discuss about whether the number of subjects in Cohort 2 could be expanded to a total of 9 subjects or not. If a decision to expand Cohort 2 to 9 subjects is taken by SMC, then MTD would be considered as dose at which ≤ 2 of 9 subjects experienced a DLT during Cycle 1.

5.6. Dose Level Escalation

Three to 6 subjects will be enrolled in 2 dose levels (Cohort 1 and Cohort 2). A total of 9 to 15 subjects will be enrolled. Dose-escalation Criteria Based on DLT is described in Table 5.1.

Cohort 1:

Subjects in Cohort 1 will be administered 600 mg/d (200 mg in the morning, 400 mg in the evening). If a DLT is observed in 1 of 3 subjects, at least 6 subjects will be treated in Cohort 1. If a DLT is observed in 0 of 3 subjects or l of 6 subjects in Cohort 1, Cohort 2 will be initiated. If a DLT is observed in 3 or more of 6 subjects in Cohort 1, Cohort 1 will be terminated and Cohort 2 will not be opened.

- If a DLT is observed in ≥ 2 of 3 subjects or ≥ 2 of 6 subjects in Cohort 1, the SMC will discuss whether a lower dose (eg, 400 mg/d) should be opened or not.

Cohort 2:

Subjects in Cohort 2 will be administered 1000 mg/d (400 mg in the morning, 600 mg in the evening). For the first 2 weeks, subjects will take 400 mg in the morning and 600 mg in the evening. Thereafter, the evening dose would be reduced to 400 mg (total 800 mg/d). Subjects who will have a dose reduction during the first 2 weeks will continue their treatment at the reduced dose level. If a DLT is observed in 0 or l of 3 subjects in Cohort 2, Cohort 2 will be expanded to 6 subjects. If a DLT is observed in 2 or 3 of 3 subjects in Cohort 2, the SMC will discuss to re-open Cohort 1 and expand up to a total of 6 subjects if Cohort 1 evaluated 3 subjects or evaluate the intermittent dose (800 mg/d). If a DLT is observed in 2 of 6 subjects in Cohort 2, the SMC will discuss

whether the number of subjects in Cohort 2 could be expanded to a total of 9 subjects or evaluate the intermittent dose (800 mg/d). If a DLT is observed in ≥ 3 of 6 subjects in Cohort 2, the SMC will discuss to re-open Cohort 1 and expand up to a total of 6 subjects if Cohort 1 evaluated 3 subjects or evaluate the intermittent dose (800 mg/d).

Table 5.1: Dose-escalation Criteria Based on DLT

Cohort 1

Incidence of DLTs	Decision	Decision, if Cohort 1 is Expanded to Total 6 Subjects
0 of 3	Cohort 2 will be opened.	Rules when Cohort 1 is re-opened: • Incidence of DLTs is 0 of 6 or 1 of 6: The MTD has been determined as Cohort 1. • 2 of 6 or 3 of 6: MTD has been exceeded at Cohort 1.[a]
1 of 3	Cohort 1 will be expanded to total 6 subjects.	• Incidence of DLTs is 1 of 6: Cohort 2 will be opened. • 2 of 6, 3 of 6, or 4 of 6: MTD has been exceeded at Cohort 1.[a]
2 of 3 or 3 of 3	The MTD has been exceeded at Cohort 1.[a]	-

DLT = dose-limiting toxicity; MTD = maximum tolerated dose.

a If DLT is observed in ≥ 2 of 3 subjects or ≥ 2 of 6 subjects in Cohort 1, the SMC will discuss whether a lower dose level (eg, 400 mg/d) should be opened or not.

Cohort 2

Incidence of DLTs	Decision	Decision, if Cohort 2 is Expanded to Total 6 Subjects
0 of 3 or 1 of 3	Cohort 2 will be expanded to total 6 subjects.	• Incidence of DLTs is 0 of 6 or 1 of 6: The MTD has been reached. • 2 of 6 subjects have DLT in Cohort 2, then SMC will discuss to expand up to a total of 9 subjects or evaluate the intermittent dose (800 mg/d). • ≥ 3 of 6 subjects in Cohort 2, the SMC will discuss to re-open Cohort 1 and expand up to a total of 6 subjects if Cohort 1 evaluated 3 subjects or evaluate the intermittent dose (800 mg/d).
2 of 3 or 3 of 3	If Cohort 1 evaluated 3 subjects, the SMC will discuss to re-open Cohort 1 and expand up to a total of 6 subjects or evaluate the intermittent dose (800 mg/d).	

DLT = dose-limiting toxicity; MTD = maximum tolerated dose; SMC = Safety Monitoring Committee.

Dose reductions and interruptions for toxicity will be permitted according to prespecified guidelines (Table 5.2 and Table 5.3).

5.7. Dose Interruptions and Reductions

Reductions or interruptions of the dose for toxicity may take place at any time during the study according to the guidelines presented in Table 5.2 and Table 5.3. Dose reduction/interruption guidelines for hematologic and non-hematologic treatment-related TEAEs are based on severity. Dose interruptions can be implemented at the discretion of the investigator to manage intolerable or clinically significant toxicity. If a dose interruption is required, study assessments should be performed as scheduled, irrespective of the study drug delay, with the exception of PK assessments, which should be deferred until treatment is resumed. Interruptions due to toxicity lasting >14 d require treatment discontinuation unless the medical monitor approves continuation.

Dose reductions should be applied in increments of 200 mg/d (1 capsule), with a minimum dose of 400 mg/d. Subjects unable to tolerate 400 mg/d (2 capsules) will be discontinued from treatment.

If toxicity requires a dosing delay or interruption for more than 3 consecutive weeks, the subject will be withdrawn from the study due to toxicity. Dose-modification guidelines for treatment-emergent toxicities as well as guidelines for their management are presented in Table 5.2 and Table 5.3. These parameters are only a guide and are not intended to supersede the clinical judgment of the investigator. All adjustments should be communicated to the Sponsor. Rechallenge with a reduced dose of pexidartinib may result in a recurrence of increased serum transaminases, bilirubin, or ALP. Monitor liver tests weekly for the first month after rechallenge.

Table 5.2: Dose Modification Guidelines for Treatment-emergent Toxicities

Event	Severity	Pexidartinib Dosage Modifications
Hepatoxicity		
Increased ALT and/or AST	>3 to 5 × ULN	• Withhold and monitor liver tests weekly. • If AST and ALT ≤3 × ULN within 4 weeks, resume at reduced dose. • If AST or ALT not ≤3 × ULN in 4 weeks, permanently discontinue pexidartinib.
	>5 to 10 × ULN	• Withhold and monitor liver tests twice weekly. • If AST and ALT ≤3 × ULN within 4 weeks, resume at reduced dose. • If AST or ALT not ≤3 × ULN in 4 weeks, permanently discontinue pexidartinib.
	>10 × ULN	• Permanently discontinue pexidartinib. • Monitor liver tests twice weekly until AST or ALT ≤5 × ULN, then weekly until ≤3 × ULN.
Increased ALP[a] and GGT	ALP >2 × ULN with GGT >2 × ULN	• Permanently discontinue pexidartinib. Monitor liver tests twice weekly until ALP ≤5 times ULN, then weekly until ≤2 × ULN.

Event	Severity	Pexidartinib Dosage Modifications
Increased bilirubin	TB >ULN to <2 × ULN or DB >ULN and <1.5 × ULN	• Withhold and monitor liver tests twice weekly. • If an alternate cause for increased bilirubin is confirmed and bilirubin <ULN within 4 weeks, resume at reduced dose. • If bilirubin not <ULN in 4 weeks, permanently discontinue pexidartinib.
	TB ≥2 × ULN or DB >1.5 × ULN	• Permanently discontinue pexidartinib. • Monitor liver tests twice weekly until bilirubin ≤ULN.
Adverse Reactions or Other Laboratory Abnormalities		
Any	Severe or intolerable	• Withhold until improvement or resolution. • Resume at a reduced dose upon improvement or resolution.

ALT = alanine aminotransferase; ALP = alkaline phosphatase; AST = aspartate aminotransferase; DB = direct bilirubin; GGT = gamma-glutamyl transferase; TB = total bilirubin; ULN = upper limit of normal.

[a] Confirm ALP elevations as liver isozyme fraction.

Table 5.3: Additional Liver Evaluation

Evaluation	Comments
Increase frequency of testing liver chemistries to twice per week, including INR, and continue until liver chemistries have stabilized, and then reduce to weekly until liver chemistries return to normal or baseline.	Investigational treatment may be started after liver function tests recover to Grade 0 to 1 or baseline level, and in consultation with Medical Monitor.
Detailed history focusing on medications and substances used: alcohol, change in medication dosages, new medications added, attention to use of acetaminophen, OTC medication use, and recreational drug use. Check for change in diet or use of dietary supplements, with particular attention to dose and duration of any herbal product.	Suspect medications will be discontinued or substituted for if possible.
Detailed medical history and physical examination seeking new abnormalities.	Evaluate abnormalities found.
Full serological evaluation for hepatitis A, B, C, and E (IgG and IgM). Check for autoimmune hepatitis with serological laboratory studies.	If viral hepatitis or autoimmune hepatitis suggested, have patient evaluated by hepatologist.
Liver ultrasound performed to evaluate liver and biliary tree.	Evaluate any abnormalities found.
Check history for exposure to chemical agents.	Remove chemical exposure and have patient seen by hepatologist.
Obtain hepatology consult if liver function continues to rise beyond 14 d.	Contact Medical Monitor.
We request that cases be discussed with the Medical Monitor as defined in the protocol whenever investigational product is being held for liver function test abnormality.	

For suspected cases of cholestatic liver injury (eg, aminotransferase increase concurrent

with hyperbilirubinemia, or liver biopsy suggesting cholestasis and/or ductopenia), patients will be followed to assess long-term outcome. Additional diagnostic and follow-up procedures might be implemented as appropriate to fully assess the event.

5.7.1. Renal Impairment

A reduced dose of 600 mg/day (200 mg in the morning and 400 mg in the evening) or 400 mg/day (200 mg in the morning and 200 mg in the evening) is recommended in study subjects with mild to severe renal impairment (calculated creatinine clearance between 15 to 89 mL/min using the Cockcroft-Gault formula).

5.8. Method of Assessing Treatment Compliance

At the study visits indicated in the Schedule of Events (Appendix 17.1), pexidartinib will be dispensed to subjects. The appropriate study personnel will document and maintain records of study drug dispensing to each subject and any returns at each study visit. Subjects will complete a dosing diary to record the number of capsules/date/time taken during each dosing cycle. At each study visit, subjects will be assessed for compliance with study drug administration, ie, return all bottles (used/unused) at least once every cycle. Further details can be found in the Study Reference Manual.

5.9. Prior and Concomitant Medications

During the study, if the use of any concomitant treatment becomes necessary (eg, for treatment of an AE), the treatment must be recorded on the subject's source document and electronic Case Report Form (eCRF), including the reason for treatment, name of the drug, dosage, date, and route of administration. All medications including prescription, over-the-counter (OTC), herbal, and other nutritional vitamins and/or supplements taken within 28 days prior to C1D1 will be recorded on the eCRF.

The use of analgesics and the regimen used will be recorded.

Subjects who are receiving concomitant warfarin should have their anticoagulation status carefully monitored. In particular, INR should be obtained just prior to initiation of pexidartinib, within 1 to 2 weeks after initiation, and periodically thereafter, and warfarin doses should be adjusted if an increase in INR is noted.

Since the possibility of a drug-drug interaction via inhibition of cytochrome P450 (CYP) is not excluded from in vitro CYP inhibition studies, caution is warranted when administering pexidartinib to subjects taking drugs that are highly dependent on CYP for metabolism and have a narrow therapeutic index. It is not known whether systemic exposure to these medications will increase while subjects are receiving pexidartinib.

Of the 5 major CYP isoforms, CYP3A4 may be involved in Phase 1 metabolism of pexidartinib, with CYP1A2 possibly playing a minor role. (see Appendix 17.3 for a list of common CYP3A4 inhibitors and inducers).

In general, strong inducers of CYP3A4 should be avoided unless clinically necessary. These include anticonvulsants, certain mycin antimicrobials, and antiretrovirals. Some

common examples include inducers such as rifampicin, carbamazepine, phenytoin, efavirenz, and nevirapine.

Avoid concomitant use of pexidartinib with moderate or strong CYP3A inhibitors or UGT inhibitors. If concomitant use with a moderate or strong CYP3A inhibitor or UGT inhibitor cannot be avoided, reduce the pexidartinib dose according to the recommendations in Table 5.4. If concomitant use of a moderate or strong CYP3A inhibitor or UGT inhibitor is discontinued, increase the pexidartinib dose (after 3 plasma half-lives of the moderate or strong CYP3A inhibitor or UGT inhibitor) to the dose that was used before starting the inhibitor.

Table 5.4: Recommended Dosage Reductions for Pexidartinib with Concomitant Use of Moderate or Strong CYP3A Inhibitors or UGT Inhibitors

Current Total Daily Dose	Modified Total Daily Dose	Administration of Modified Total Daily Dose
800 mg	400 mg	200 mg twice daily
600 mg	400 mg	200 mg twice daily
400 mg	200 mg	200 mg once daily

5.9.1. Hormonal Contraceptives

Pexidartinib has been indicated to be a moderate CYP3A4 inducer, as concurrent administration of pexidartinib decreased the AUCinf of the CYP3A4 substrate midazolam by 57%. As the hormonal contraceptive ethinyl estradiol is a CYP3A4 substrate, there is a potential that exposure of ethinyl estradiol may decrease on concurrent administration with pexidartinib. As pexidartinib may cause embryo-fetal harm when administered to a pregnant woman, females of reproductive potential should be advised to use an effective, non-hormonal method of contraception during treatment with pexidartinib and for 1 month after the last dose. Males with female partners of reproductive potential should be advised to use an effective method of contraception during treatment with pexidartinib and for 1 month after the last dose. Female partners of male patients should concurrently use effective contraceptive methods (hormonal or non-hormonal).

5.9.2. Acid-reducing Agents

Avoid the concomitant use of proton pump inhibitors (PPIs) while taking pexidartinib. As an alternative to a PPI, administer pexidartinib 2 hours before or 2 hours after taking a locally-acting antacid, or if using a histamine 2 (H2)-receptor antagonist, administer pexidartinib at least 2 hours before or 10 hours after taking an H2-receptor antagonist.

The following medications and products will be prohibited:

- Other anticancer therapy including cytotoxics, targeted agents, immunotherapy, or endocrine therapy
- Other investigational agents
- Because pexidartinib is primarily metabolized by CYP3A4 and grapefruit juice is a CYP3A4 inhibitor, foods or beverages containing grapefruit should be avoided for the duration of the study.

5.10. Subject Withdrawal/Discontinuation

5.10.1. Reasons for Withdrawal

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

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

- Disease progression (radiographic progression)
- Clinical progression (provide date)
- AE
- Lost to follow-up
- Death
- Study terminated by the Sponsor
- Protocol violation (specify)
- Withdrawal by subject
- Other (eg, discretion of the investigator)

5.10.2. Withdrawal Procedures

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

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

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

5.10.3. Subject Replacement

Subjects who are withdrawn from the study prior to completing Cycle 1 for any reason other than a DLT will be replaced. Subject numbers must not be re-used.

Subjects who receive < 75% of the planned dose during the DLT evaluation period will not be considered evaluable and need to be replaced.

6. STUDY PROCEDURES

A Schedule of Events in tabular format is provided in Appendix 17.1.

Descriptions of the specific study procedures are provided in the following subsections. Additional details are provided in the Study Reference Manual or Laboratory Manual as applicable.

6.1. Screening

6.1.1. Day –28 to Day –1

The following procedures must be performed within the 28-day period before first dose unless otherwise specified, and the results must be obtained and evaluated for eligibility prior to the C1D1 visit:

- Informed consent
- Medical history comprising all prior and current medical history and smoking history
- Demographics, eg, birth date, sex, race, primary cancer history, significant medical history information, and prior treatment history for cancer
- Concomitant medications
- Height and weight
- ECOG PS
- AE assessment

6.1.2. Day –21 to Day –1

The following procedures must be performed within the 21-day period before first dose:

- ECHO or multi-gated acquisition (MUGA) scanning (within 21-day period before first dose)
- Computed tomography (CT)/magnetic resonance imaging (MRI) (MRI of the affected joint for subjects with TGCT is mandatory*) (within 21-day period before first dose)

* For TGCT subjects, MRI of the affected joint is mandatory and the CT or MRI scans of the chest, abdomen, and pelvis are not required, and to be done upon the investigator's discretion.

6.1.3. Day –14 to Day –1

The following procedure must be performed within the 14-day period before first dose:

- Pregnancy testing (as applicable within 14-day period before first dose)

6.1.4. Day –7 to Day –1

The following procedures must be performed within the 7-day period before first dose:

- Vital signs, including blood pressure, pulse rate, respiratory rate, and temperature (within 7-day period before first dose)
- Complete physical examination (within 7-day period before first dose)
- Clinical laboratory tests – serum chemistry, hematology, liver function, hormone testing (as applicable), coagulation, and urinalysis (within 7-day period before first dose except for coagulation tests)
- 12-lead ECG (within 7-day period before first dose)

6.2. Randomization

Not applicable.

6.3. Treatment Period

6.3.1. Cycle 1

6.3.1.1. Cycle 1, Day 1 (C1D1; Week 1)

To be performed within 3 days before the first morning dose of study drug:

- Dispensing of study drug and subject diary
- Vital signs, including blood pressure, pulse rate, respiratory rate, and temperature
- Physical examination
- 12-lead ECG
- Clinical laboratory tests – serum chemistry, liver function, urinalysis, coagulation, and hematology
- Blood sampling for PD analysis

To be performed before the first morning dose of study drug:

- AE assessment
- Concomitant medications
- Blood sampling for PK analysis

To be performed after the first morning dose of study drug:

- Blood sampling for PK analysis at the following time points: 0.5, 1, 2, 4, and 8 h after the first morning dose (before the evening dose)

6.3.1.2. Cycle 1, Day 2 (C1D2; Week 1)

- AE assessment
- Concomitant medications

- Blood sampling for PK analysis at 24 h after the first morning dose (before the next morning dose)

6.3.1.3. Cycle 1, Day 8 (C1D8; Week 2) ± 2 days

- Vital signs, including blood pressure, pulse rate, respiratory rate, and temperature
- Physical examination
- AE assessment
- Clinical laboratory tests – serum chemistry, hematology, liver function and urinalysis
- Concomitant medications
- Blood sampling for PK analysis before the morning dose

6.3.1.4. Cycle 1, Day 15 (C1D15; Week 3) ± 2 days

- Vital signs, including blood pressure, pulse rate, respiratory rate, and temperature
- Physical examination
- AE assessment
- Clinical laboratory tests – serum chemistry, hematology, liver function and urinalysis
- Concomitant medications
- Blood sampling for PK analysis before the morning dose
- Blood sampling for PD analysis before the morning dose

<u>To be performed after the morning dose of study drug:</u>

- Blood sampling for PK analysis at the following time points: 0.5, 1, 2, 4, and 8 h after the morning dose (before the evening dose)

6.3.1.5. Cycle 1, Day 22 (C1D22; Week 4) ± 2 days

- Vital signs, including blood pressure, pulse rate, respiratory rate, and temperature
- Physical examination
- AE assessment
- Clinical laboratory tests – serum chemistry, hematology, liver function and urinalysis
- Concomitant medications
- Blood sampling for PK analysis before the morning dose

6.3.2. Cycle 2

6.3.2.1. Cycle 2, Day 1 (C2D1; Week 5) ± 2 days

- Dispensing of study drug and subject diary
- Vital signs, including blood pressure, pulse rate, respiratory rate, and temperature
- Physical examination
- ECOG PS
- ECG
- ECHO/MUGA
- AE assessment
- Clinical laboratory tests – serum chemistry, hematology, liver function, urinalysis, and hormone testing
- Concomitant medications
- Blood sampling for PK analysis before the morning dose
- Blood sampling for PD analysis before the morning dose

6.3.2.2. Cycle 2, Day 8 (C2D8; Week 6) ± 2 days

- Clinical laboratory tests – liver function
- AE assessment
- Concomitant medications

6.3.2.3. Cycle 2, Day 15 (C2D15; Week 7) ± 2 days

- Vital signs, including blood pressure, pulse rate, respiratory rate, and temperature
- Physical examination
- AE assessment
- Clinical laboratory tests – serum chemistry, hematology, liver function, urinalysis and hormone testing
- Concomitant medications

6.3.2.4. Cycle 2, Day 22 (C2D22; Week 8) ± 2 days

- Clinical laboratory tests – liver function
- AE assessment
- Concomitant medications

6.3.3. Cycle 3

6.3.3.1. Cycle 3, Day 1 (C3D1; Week 9) ± 2 days

- Dispensing of study drug and subject diary
- Vital signs, including blood pressure, pulse rate, respiratory rate, and temperature
- Physical examination
- CT/MRI (MRI of the affected joint for subjects with TGCT is mandatory*)
- ECOG PS
- ECG
- Clinical laboratory tests – serum chemistry, hematology, liver function, and urinalysis
- AE assessment
- Concomitant medications

*For TGCT subjects, MRI of the affected joint is mandatory and the CT or MRI scans of the chest, abdomen, and pelvis are not required, and to be done upon the investigator's discretion.

6.3.3.2. Cycle 3, Day 8 (C3D8; Week 10) ± 2 days

- Clinical laboratory tests –liver function
- AE assessment
- Concomitant medications

6.3.3.3. Cycle 3, Day 15(C3D15; Week 11) ± 2 days

- Clinical laboratory tests –liver function
- AE assessment
- Concomitant medications

6.3.4. Cycle 4

6.3.4.1. Cycle 4, Day 1 (C4D1; Week 13) ± 7 days

- Dispensing of study drug and study diary
- Vital signs, including blood pressure, pulse rate, respiratory rate, and temperature
- Physical examination
- ECOG PS
- ECG
- Clinical laboratory tests – serum chemistry, hematology, liver function, and urinalysis

- AE assessment
- Concomitant medications

6.3.4.2. Cycle 4, Day 15 (C4D15; Week 15) ± 7 days

- Clinical laboratory tests –liver function
- AE assessment
- Concomitant medications

6.3.5. Cycle 5 and thereafter (before entering extension part)

6.3.5.1. Cycle 5, Day 1 (C5D1+; Week 17) and thereafter (before entering extension part) ± 7 days

- Dispensing of study drug and study diary
- Vital signs, including blood pressure, pulse rate, respiratory rate, and temperature
- Physical examination
- CT/MRI (MRI of the affected joint for subjects with TGCT is mandatory*)
- ECOG PS
- ECG
- Clinical laboratory tests – serum chemistry, hematology, liver function, and urinalysis
- AE assessment
- Concomitant medications

*For TGCT subjects, MRI of the affected joint is mandatory and the CT or MRI scans of the chest, abdomen, and pelvis are not required, and to be done upon the investigator's discretion.

6.3.6. Treatment Visits During Extension part

6.3.6.1. Every 4 weeks ± 7 days

- Dispensing of study drug and subject diary
- Clinical laboratory tests – serum chemistry, hematology, liver function, and coagulation
- AE assessment

6.3.6.2. Every 12 weeks ± 7 days

- Dispensing of study drug and subject diary
- Vital signs, including blood pressure, pulse rate, respiratory rate, and temperature
- Physical examination

- ECG
- ECHO/MUGA
- Clinical laboratory tests – serum chemistry, hematology, liver function, coagulation, and urinalysis
- CT/MRI (MRI of the affected joint for subjects with TGCT is mandatory*)
- Serum pregnancy test
- AE assessment
- Concomitant medications

*For TGCT subjects, MRI of the affected joint is mandatory and the CT or MRI scans of the chest, abdomen, and pelvis are not required, and to be done upon the investigator's discretion.

6.4. End of Treatment

The date of discontinuation of treatment is defined as the date of decision by the investigator. The following assessments will be performed at the end of treatment visit (within 3 days after the date of discontinuation). If the assessments at the end of treatment are performed in the treatment period, they can be considered to be the end of treatment data and there is no need to repeat them.

- AE assessment
- Vital signs, including blood pressure, pulse rate, respiratory rate, and temperature
- Physical examination
- MUGA
- Clinical laboratory tests – serum chemistry, hematology, liver function, urinalysis, coagulation, and hormone testing
- 12-lead ECG
- CT/MRI (MRI of the affected joint for subjects with TGCT is mandatory*)
- ECOG PS
- Concomitant medications
- Weight
- Pregnancy test

*For TGCT subjects, MRI of the affected joint is mandatory and the CT or MRI scans of the chest, abdomen, and pelvis are not required, and to be done upon the investigator's discretion.

6.5. Follow-up

The follow-up visit is scheduled at 28 days (± 7 days) after the last administration of pexidartinib. If the subject begins another anticancer therapy before the end of the

28 days (± 7 days), every effort will be made to complete all the follow-up visit assessments prior to commencing the new therapy. In case of unresolved AEs, the investigator will follow the AEs until the event has resolved or the condition has stabilized as possible. If the assessments at end of treatment or treatment period are performed within this period, they can be considered to be the follow-up data and there is no need to repeat them.

The following information will be collected at the follow-up visit:

- AE assessment
- Concomitant medications

6.6. Pharmacogenomic sample collection visit

Participation in this part of the study is optional for all subjects. Pharmacogenomic sample may also be collected from discontinued subjects who provide consent, and could be collected anytime during study conduct. For ongoing subjects, this visit could be combined with subjects' current study visit schedule.

- Collect signed informed consent for pharmacogenomics study participation
- Collect a single blood sample (10 mL)

7. EFFICACY ASSESSMENTS

Efficacy assessments will be based on tumor assessments to be performed at the screening period and at least every 2 cycles (± 7 days) in the first 4 cycles after C1D1 and thereafter at least every 3 cycles (± 7 days) if the subject remains in the study therapy. The clinical activity of pexidartinib will be assessed by evaluating tumor response. Tumor response will be evaluated using RECIST Version 1.1. The CT or MRI (spiral CT or MRI with ≤ 5 mm cuts) of brain, chest, abdomen, and pelvis will be used for the tumor assessment unless another modality of disease assessment is necessary for the lesions at the screening period. Every effort should be made to use the same assessment modality for all assessments for each subject. However, if there is no brain metastasis at the time of screening, CT or MRI should be performed only be done when symptoms associated with brain metastasis occur during the study period. If no clinical symptoms are observed, brain CT or MRI is not mandatory during the study period. The following efficacy variables will be assessed:

- ORR DCR
- Response duration
- Duration of SD
- TTR
- Percentage of change in target lesion(s)

7.1. Tumor Imaging

The same tumor imaging assessment as at the time of screening by CT or MRI scans will be performed at least every 2 cycles (± 7 days) in the first 4 cycles after C1D1, thereafter at least every 3 cycles (± 7 days) if the subject remains in the study therapy, at every 12 weeks (± 7 days) during extension part of the study, and the end of treatment visit. The assessment will be conducted before Day 1 of each cycle as possible. The CT or MRI scans of the chest, abdomen, and pelvis are mandatory. However, if there is no brain metastasis at the time of screening, CT or MRI should be performed only when symptoms associated with brain metastasis occur. If no clinical symptoms are observed, a brain CT or MRI is not mandatory.

For subjects with TGCT, non-contrast MRI of the affected joint will be performed at the study visits indicated in the Schedule of Events (Appendix 17.1)*.

*For TGCT subjects, MRI of the affected joint is mandatory and the CT or MRI scans of the chest, abdomen, and pelvis are not required, and to be done upon the investigator's discretion.

7.2. Efficacy Endpoints

7.2.1. Primary Efficacy Endpoints

Not applicable.

7.2.2. Secondary Efficacy Endpoints

Not applicable.

7.2.3. Exploratory Efficacy Endpoints

Not applicable.

7.2.4. Appropriateness of Selected Efficacy Endpoints

Not applicable.

8. PHARMACOKINETIC/PHARMACODYNAMIC ASSESSMENTS

8.1. Pharmacokinetic Endpoint(s)

The PK/PD sampling will be performed at the study visits indicated in the Schedule of Events (Appendix 17.1). Detailed instructions on collection, processing, handling, storage, and sample shipment are described in the separate Laboratory Manual.

Blood samples of approximately 3 mL for PKs (5 mL for PK and PD on C1D1, and C1D15, C2D1) analyses will be collected at the time points specified in Table 8.1.

The exact time of dose administration should be recorded along with the corresponding PK blood samplings. The exact time of the preceding doses should also be recorded.

Table 8.1: Pharmacokinetics Sampling Time Points

Cycle	Day	Sampling Time Point (Acceptable Range)
Cycle 1	Day 1	Predose
		0.5 h after administration (± 10 minutes)
		1 h after administration (± 15 minutes)
		2 h after administration (± 15 minutes)
		4 h after administration (± 20 minutes)
		8 h after administration (± 20 minutes)
	Day 2	24 h after administration (± 60 minutes)
		Sample should be collected before the morning dose
	Day 8	Predose (± 2 days)
	Day 15	Predose
		0.5 h after administration (± 10 minutes)
		1 h after administration (± 15 minutes)
		2 h after administration (± 15 minutes)
		4 h after administration (± 20 minutes)
		8 h after administration (± 20 minutes)
	Day 22	Predose (± 2 days)
Cycle 2	Day 1	Predose (± 2 days)

The plasma PK parameters of pexidartinib and its metabolite listed in Table 8.2 for each subject will be estimated using standard non-compartmental methods. Primary PK parameters are the area under the plasma-concentration-time curve from time 0 to 8 h ($AUC_{0\text{-}8h}$), Cmax, and Tmax for Day 1 and Day 15.

Table 8.2: Pharmacokinetics Parameters

Day 1	Peak drug concentration (Cmax) Time of maximum observed concentration (Tmax) Area under the plasma concentration-time curve from time 0 to 8 h (AUC_{0-8h})
Day 15	Maximum plasma concentration (Cmax) Time of maximum observed concentration (Tmax) Area under the plasma concentration-time curve from time 0 to 8 h (AUC_{0-8h})

8.2. Pharmacodynamic Endpoints

Plasma for circulating PD biomarkers will be collected once per day on the same days when PK blood sample(s) are drawn (eg, predose) and will be analyzed for exploratory biomarkers of monocyte or macrophage activities, including CSF-1 and adiponectin.

Blood samples for PK/PD (5 mL for PK and PD on C1D1, and C1D15, C2D1) analyses will be collected at the time points specified in Appendix 17.1.

Blood samples collected at specified time points will be analyzed for plasma CSF-1 and adiponectin indicated in the Schedule of Events (Appendix 17.1). No formal statistical analysis of PD variables will be performed. The PD data will be listed by cohort and summarized with descriptive statistics by dose and visit.

8.3. Biomarker Endpoints

Not applicable.

8.4. Immunogenicity

Not applicable.

8.5. Pharmacogenomic Analysis

A single blood sample (10 mL) for pharmacogenomics analysis will be collected from each subject who consents to this test. Pharmacogenomic samples may also be collected from discontinued subjects who provide consent. Participation in this part of the study is optional for all subjects.

Pharmacogenomic samples will be analyzed for UGT1A4 genotype. Additional genotyping may be done for genes involved in safety of pexidartinib. Additionally, samples may be analyzed for genes involved in pexidartinib-related signaling pathways, or to examine diseases or physiologic processes related to pexidartinib. DNA samples will not be immortalized or sold to anyone. This information may be useful in increasing the knowledge of differences among individuals in the way they respond to the study drug, as well as helping in the development of new drugs or improvement of existing drugs.

Specimen shipping and handling details will be included in the laboratory manual.

9. SAFETY EVALUATION AND REPORTING

9.1. Adverse Event Collection and Reporting

All clinical AEs (see Section 9.4.1 for definitions) occurring after the subject signs the ICF and up to the Follow-up visit after the last dose of study drug (ie, the Follow-up period), whether observed by the investigator or reported by the subject, will be recorded on the AE eCRF page. Medical conditions (including 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 the medical history.

All AEs and SAEs are to be reported according to the procedures indicated in Section 9.5.

All laboratory results, vital signs, and ECG findings should be appraised by the investigator to determine their clinical significance. All abnormal laboratory results considered to be clinically significant by the investigator must be recorded as AEs on the eCRF, and if serious, reported as SAEs following the procedures indicated in Section 9.5.

Disease progression is a study endpoint and consequently, should not be reported as an AE or SAE. However, when a subject dies from disease progression without other immediate causes, "disease progression" should be reported as a SAE. Any serious, untoward event that occurs subsequent to the reporting period that the investigator assesses as related to the study drug should also be reported and managed as an SAE. At each visit, the investigator will determine whether any AEs have occurred by evaluating the subject. The AEs can be directly observed, reported spontaneously by the subject, or by questioning the subject at each study visit. 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 9.4.3 and 9.4.4. The investigator's assessment must be clearly documented in the study site's source documentation with the investigator's signature.

Always report diagnosis as an 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 a 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. Preplanned (prior to signing the ICF) procedure or treatment requiring hospitalization for pre-existing conditions that do not worsen in severity should not be reported as SAEs (see Section 9.4.2). For deaths, the underlying or immediate cause of death should always be reported as an SAE.

The investigator should follow the subjects with AEs until the events have been resolved or the condition has been stabilized. In case of unresolved AEs including significant abnormal laboratory values at the end of study assessment, these events will be followed up until resolution or becoming not clinically relevant.

9.2. Safety Endpoint Events

Safety endpoints include DLTs, SAEs, TEAEs, physical examination findings (including ECOG PS), vital sign measurements, standard clinical laboratory parameters, ECG parameters, and ECHO/MUGA findings. All TEAEs will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Event (NCI-CTCAE) Version 4.0.

9.3. Events of Special Interest

9.3.1. Combined Elevations of Aminotransferases and Bilirubin

Combined elevations of aminotransferases and bilirubin, either serious or nonserious and whether or not causally related, meeting the laboratory criteria of a potential Hy's Law case (ALT or AST $\geq 3 \times$ ULN with simultaneous total bilirubin $\geq 2 \times$ ULN) should always be reported to the Sponsor using a Serious Adverse Event Report (SAVER) Form or a special collection of eCRF along with the investigator's assessment of seriousness, causality, and a detailed narrative. These events should be reported within 24 h of the investigator's awareness of the events.

If the subject discontinues the study drug due to liver enzyme abnormalities, the subject will have additional clinical and laboratory evaluations as described in Section 5.10 in order to determine the cause and severity of the potential liver injury.

9.4. Adverse Event

9.4.1. Definition of Adverse Event

An AE is any untoward medical occurrence in a subject administered a pharmaceutical product 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 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 (International Council for Harmonisation [ICH] E2A Guideline. Clinical Safety Data Management: Definitions and Standards for Expedited Reporting, Oct 1994).

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

9.4.2. Serious Adverse Event

SAE is any untoward medical occurrence 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

- 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 that hypothetically might have caused death if it was 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 the 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. Preplanned (prior to signing the ICF) procedures or treatments requiring hospitalization for pre-existing conditions that do not worsen in severity are not SAEs.

9.4.3. Severity Assessment

All AEs will be graded (1 to 5; see below) according to the NCI-CTCAE Version 4.0:

- Grade 1: Mild. Awareness of sign or symptom, but easily tolerated, ie, does not interfere with subject's usual function
- Grade 2: Moderate. Discomfort enough to cause interference with usual activity
- Grade 3: Severe. Incapacitating with inability to work or do usual activity, ie, interferes significantly with subject's usual function
- Grade 4: Life-threatening or disabling AE; urgent intervention indicated
- Grade 5: Death related to AE

Severity versus Seriousness: Severity is used to describe the intensity of a specific event while the event itself, however, may be of relatively minor medical significance (such as severe headache). This is not the same as "seriousness", which is based on subject/event outcome at the time of the event. For example, the NCI-CTCAE Grade 4 (life-threatening consequences, urgent intervention indicated) is assessed based on unique clinical descriptions of severity for each AE, and these criteria may be different from those used for the assessment of AE seriousness. An AE assessed as Grade 4 based on the NCI-CTCAE grades may or may not be assessed as serious based on the seriousness criteria.

9.4.4. 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 the 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 the study drug administration, and is a known reaction to the drug under study or its chemical group, or can be predicted by known pharmacology.

- Not Related:
  - 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).

9.4.5. Actions to be Taken Regarding the Study Drug

The following criteria should be applied to decide the action to be taken regarding the study drug:

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

9.4.6. Other Actions to be Taken for Event

- None

  –No treatment was required

- Medication required

  –Prescription and/or OTC medication was required to treat the AE

- Hospitalization or prolongation of hospitalization required

  –Hospitalization was required or prolonged due to the AE, whether or not medication was required

- Other

9.4.7. Adverse Event Outcome

- Recovered/Resolved
  - The subject fully recovered from the AE with no residual effect observed
- Recovered/Resolved with Sequelae

  - The residual effects of the AE are still present and observable
  - Include sequelae/residual effects
- Not Recovered/Not Resolved
  - The AE itself is still present and observable
- Fatal
  - Fatal should be used when death is a direct outcome of the AE
- Unknown

9.5. Serious Adverse Events Reporting–Procedure For Investigators

All AEs and SAEs will be reported in the eCRF.

The following types of events should be reported by the investigator on the SAE form of eCRF or on a SAVER Form in case of eCRF down time within 24 h of awareness:

- SAEs (see Section 9.4.2)
- Hepatic events meeting combination abnormalities [ALT or AST $\geq 3 \times$ ULN with simultaneous total bilirubin $\geq 2 \times$ ULN] (potential Hy's Law case), both serious and nonserious (see Section 9.3 for additional details)

All events (serious and non-serious) must be reported along with the investigator's assessment of the event's seriousness, severity, and causality to the study drug. A detailed narrative summarizing the course of the event, including its evaluation, treatment, and outcome should be provided. Specific or estimated dates of event onset, treatment, and resolution should be included when available. Medical history, concomitant medications, and 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 study site and should not be submitted to the Sponsor for SAE reporting purpose.

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.

See Appendix 17.4 for contact information for SAE reporting. Please call the local SAE Hotline (see Study Reference Manual) or your study monitor for any questions on SAE reporting.

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

Daiichi Sankyo and/or QuintilesIMS will inform investigators, Institutional Review Boards (IRBs), and regulatory authorities of any Suspected Unexpected Serious Adverse Reactions (SUSARs) occurring in other study sites or other studies of the study drug, as appropriate per local reporting requirements.

In Taiwan, upon receipt of the Sponsor's notification of SUSARs, it is the investigator's responsibility to report SUSARs to IRBs according to reporting guideline of the IRBs.

9.7. Exposure In Utero During Clinical Studies

Daiichi Sankyo and/or QuintilesIMS must be notified of any subject who becomes pregnant while receiving or within the Follow-up period (28 ± 7 days after the last dose of the study drug).

Although pregnancy is not technically an AE, all pregnancies must be followed until conclusions being reached to determine their outcomes. 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 nonserious, should be reported in accordance with the study procedures. If the outcome of the pregnancy meets the criteria for immediate classification as a SAE (ie, postpartum 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 9.5.

9.8. Clinical Laboratory Evaluations

Clinical laboratory evaluations will be performed at the study visits indicated in the Schedule of Events (Appendix 17.1). Eligibility decisions will be based on local laboratory values. Clinical laboratory evaluations will be performed as outlined in Table 9.1.

Blood samples for analysis of the following clinical chemistry, hematologic, coagulation, and hormone parameters will be collected.

Table 9.1: Clinical Laboratory Evaluations

Laboratory Tests	Parameters
Clinical chemistry	Sodium, potassium, chloride, calcium, phosphorus, carbon dioxide, total protein, albumin, triglycerides[a], total cholesterol[a], high density lipoprotein-cholesterol[a], low density lipoprotein-cholesterol[a], glucose[a], uric acid, blood urea nitrogen, lactate dehydrogenase, and creatinine
Liver function	Alkaline phosphatase, total bilirubin, direct bilirubin, ALT, AST, and GGT
Hematology	Red blood cell count, hemoglobin, white blood cell count with differential (neutrophils, lymphocytes, monocytes, eosinophils and basophils), hematocrit, and platelet count
Coagulation	Prothrombin time, activated partial thromboplastin time, and INR
Hormone	Women: FSH, LH, progesterone, and estradiol Men: FSH, LH, and testosterone
Urine samples will be obtained for analysis of the following parameters:	
Urinalysis (dipstick and microscopic analysis)	pH, ketones/acetone, protein/albumin, hemoglobin/blood, glucose/sugar, red blood cells, white blood cells, epithelial cells, bacteria, casts, crystals, and nitrites

ALT = alanine aminotransferase; AST = aspartate aminotransferase; GGT = gamma glutamyl transferase, FSH = follicle-stimulating hormone; INR = International Normalized Ratio; LH = luteinizing hormone.
a Fasting is recommended but not required.

9.9. Vital Signs

Vital signs, including systolic/diastolic blood pressure, pulse rate, and temperature will be measured in accordance with institutional standards and generally should be performed before invasive procedures, eg, blood draws. Vital signs and weight will be measured at the indicated study visits as in the Schedule of Events (Appendix 17.1). Height will be measured at screening period only.

Blood pressure and pulse rate will be measured after the subject has rested in a recumbent position for 5 minutes or more.

Information will be recorded in the eCRF, including whether or not being measured, dates of measurement, and measurement results for the following items:

- Systolic blood pressure
- Diastolic blood pressure
- Pulse rate

- Respiratory rate
- Body temperature
- Height
- Body weight

9.10. Electrocardiograms

A standard 12-lead ECG will be obtained at the study visits indicated in the Schedule of Events (Appendix 17.1).

The ECG will be measured after the subject has rested in a recumbent position for 5 minutes or more. Whether or not the measurement is performed, date of measurement, results, and findings for the following parameters will be recorded in the eCRF. At the visits when ECGs are to be performed, subjects should be told not to take the morning dose of the study drug. The ECG should be performed prior to blood sampling procedures.

Standard supine 12-lead ECGs in triplicate will be performed as specified in the Schedule of Events (Appendix 17.1). The ECG recordings must be performed using a standard high-quality and high-fidelity electrocardiography machine equipped with computer-based interval measurements. Standard ECG parameters will be measured, including heart rate, RR, PR, QT, QTcF intervals, and QRS duration. All ECGs must be evaluated by the investigator or delegated physician for the possible presence of abnormalities.

9.11. Physical Examinations

Physical examinations will be performed by a qualified individual such as the investigator at the study visits indicated in the Schedule of Events (Appendix 17.1).

Physical examination findings including ECOG PS will be used to evaluate the following body systems/organs: general appearance, dermatological, head and eyes, ears, nose, mouth, and throat, pulmonary, cardiovascular, abdominal, genitourinary (optional), lymphatic, musculoskeletal/extremities and neurological. Weight and height will also be recorded in kilograms and centimeters, respectively.

9.12. Other Examinations

9.12.1. Echocardiogram

A resting ECHO or MUGA scan will be performed at the study visits indicated in the Schedule of Events (Appendix 17.1) to evaluate the subjects' cardiac function throughout their study participation. In this protocol, "ECHO scan" and "MUGA scan" will be used interchangeably. The choice of whether to perform ECHO or MUGA scan will be based on the preference of the investigator, but the platforms should not be switched during the course of a subject's study participation. Clinically important findings, including the left ventricular ejection fraction, will be recorded in the appropriate eCRF.

9.12.2. Pregnancy Test

For female subjects of childbearing potential only, a serum pregnancy test (β-human chorionic gonadotropin) will be performed at the study visits indicated in the Schedule of Events (Appendix 17.1).

For postmenopausal subjects (no childbearing potential, as indicated by an elapse of at least 12 months after the last menstruation) or female subjects who have no possibility of pregnancy due to sterilization surgery, etc. pregnancy test will not be required.

Female subjects who have been amenorrheic for 12 months or longer due to medical reasons other than sterilization surgery (eg, effect of medication) will be regarded as women of childbearing potential and they are required to undergo the pregnancy test.

10. OTHER ASSESSMENTS

No other assessments will be performed.

11. STATISTICAL METHODS

11.1. Analysis Sets

11.1.1. Enrolled Analysis Set

The Enrolled Analysis Set will include all subjects who signed the ICF and were enrolled in the study. The Enrolled Analysis Set will be used to summarize and describe the subject disposition and deaths, unless stated otherwise.

11.1.2. Efficacy Analysis Set

The Efficacy Analysis Set will include all subjects who received at least 1 dose of pexidartinib and had pretreatment and posttreatment efficacy data.

11.1.3. Dose-limiting Toxicity Evaluable Set

The DLT-Evaluable Set will include all subjects who experienced a DLT during Cycle 1 or received at least 75% of the planned doses of treatment during the DLT observation period (Cycle 1).

11.1.4. Safety Analysis Set

The Safety Analysis Set will include all subjects who received at least 1 dose of pexidartinib. Subjects will be summarized according to the treatment actually received.

11.1.5. Pharmacokinetic Analysis Set

The PK Analysis Set will include all subjects in the Enrolled Analysis Set who received at least 1 dose of pexidartinib and had at least 1 evaluable postdose plasma concentrations of pexidartinib or its metabolite without major protocol deviations or events (eg, vomiting until 4 h post dose, incomplete dosing, disallowed concomitant medications, etc) affecting PK.

11.1.6. Pharmacodynamics Analysis Set

The PD Analysis Set will include all subjects in the Enrolled Analysis Set who received at least 1 dose of pexidartinib and had a post dose PD measurement without major protocol deviations or events (eg, vomiting, incomplete dosing, disallowed concomitant medications, etc) affecting PD.

11.2. General Statistical Considerations

The data cut-off for the primary analysis will occur after all subjects have either discontinued the study or completed at least 4 cycles. After the primary analysis, the main study will be closed and the data will be followed in the extension part. Data collected in the extension part will be reported separately from the clinical study report.

Data will be listed and summarized using Statistical Analysis System (SAS®) Version 9.2 or higher (SAS Institute, Inc., Cary, North Carolina) according to the Sponsor-agreed

reporting standards, where applicable. Complete details will be documented in the Statistical Analysis Plan (SAP).

The following descriptive statistics will be used to summarize the study data on the basis of their nature unless otherwise specified:

- Continuous variables: number of nonmissing observations, mean, standard deviation, median, minimum, and maximum as well as geometric means and geometric coefficient of variation for Cmax and AUC PK parameters
- Categorical variables: frequencies and percentages
- Time-to-event variables: number of nonmissing observations (N), median, minimum and maximum. Kaplan-Meier event rates may also be provided if applicable for specific time-to-event variables

Assessments of change from baseline to post-treatment or the ratio of post-treatment to baseline will include only those subjects with both baseline and post-treatment measurements. The last nonmissing value of a variable taken before the first dose of study drug will be used as the baseline value, unless otherwise specified. In general, missing or dropout data will not be imputed for the purpose of data analysis, unless otherwise specified. Safety and efficacy data from the extension part will be summarized using descriptive statistics as tables and listings, if applicable. Further description of the statistical methods and analyses will be provided in the SAP.

11.3. Study Population Data

Subject disposition and reasons of ending the treatment and discontinuing from the study will be summarized and listed for subjects in the Enrolled Analysis Set.

Demographic and baseline characteristics such as age, sex, race, ethnicity, baseline ECOG PS, histology, cancer stage, best response to prior chemotherapy, lines of prior regimens, and prior treatment type will be summarized for subjects in the Safety Analysis Set.

11.4. Statistical Analyses

11.4.1. Efficacy Analyses

The tumor response will be evaluated using RECIST Version 1.1. Response will be collected in the form of 4 categories: progressive disease (PD), SD (a minimum of 8 weeks from the first dosing date), CR, and PR.

All efficacy variables will be listed and summarized. The number and percentage of subjects in each category will be summarized.

Objective Response Rate and Disease Control Rate

The number and proportion of subjects who achieve objective tumor response (CR or PR) or SD will be summarized. The ORR and DCR will be calculated using point estimates along with 95% exact binomial confidence intervals (CIs).

Duration of Response or Duration of Stable Disease

Duration of response for responders (CR or PR) is defined as the time interval between the date of the earliest qualifying response and the date of progressive disease or death for any cause, whichever occurs earlier. For subjects who are alive without disease progression following the qualifying response, duration of response will be censored on the date of the last evaluable tumor assessment or the last follow-up for disease progression.

The TTR is defined as the time from the date of the first dose to the date at which criteria are first met for CR or PR.

Duration of SD is defined as the time interval, in the absence of either CR or PR that will be calculated between the date of the first administration of the study drug and the date of progressive disease. For subjects who are alive without disease progression, duration of SD will be censored on the date of the last evaluable tumor assessment.

Duration of response or duration of SD will be summarized.

11.4.2. Pharmacokinetic/Pharmacodynamic Analyses

11.4.2.1. Pharmacokinetic Analyses

The PK analyses will be performed on the PK Analysis Set. Plasma concentration-time data for pexidartinib and its metabolite will be listed, plotted, and summarized using descriptive statistics by cohort at each point and in the study period.

The PK parameters of pexidartinib and its metabolite will be listed and summarized using descriptive statistics.

Plasma concentration data will be used to perform a population PK modeling. The influences of intrinsic or extrinsic factor will be assessed in the population PK analysis.

If performed, results of population PK analyses will be reported separately (ie, not in the Clinical Study Report).

11.4.2.2. Pharmacodynamic Analyses

Explorative analyses for biomarkers will be listed and summarized using descriptive statistics.

11.4.2.3. Biomarker Analyses

Not applicable.

11.4.3. Safety Analyses

The safety profile will be based on AEs, physical examination findings, vital sign measurements, clinical laboratory measurements, ECG recordings, and ECHO/MUGA findings. The AEs will be graded according to the NCI-CTCAE Version 4.0. In the dose-escalation part, the incidence of DLTs will also be evaluated.

Safety analyses in general will be descriptive and be presented in tabular format with the appropriate summary statistics. The number of DLTs identified among the DLT-evaluable subjects in the DLT-Evaluable Set will be listed and summarized.

11.4.3.1. Adverse Event Analyses

A TEAE is defined as an AE that emerges during the treatment period (from first dose date until Follow-up visit after the last dose of study drug), having been absent at pretreatment; or reemerges during treatment, having been present at baseline but stopped prior to treatment; or worsens in severity after starting treatment relative to the pretreatment state, when the AE is continuous.

The number and percentage of subjects reporting TEAEs will be tabulated by the worst NCI-CTCAE grade, System Organ Class (SOC), and Preferred Term.

Similarly, the number and percentage of subjects reporting treatment-emergent SAEs will be tabulated, as well as the TEAEs/SAEs considered related to pexidartinib. A by-subject AE (including TEAE) data listing will be provided including, but not limited to, verbatim term, Preferred Term, SOC, NCI-CTCAE grade, and relationship to study drug.

Deaths, other SAEs, and other significant AEs, including those leading to permanent discontinuation from pexidartinib, will be listed.

11.4.3.2. Clinical Laboratory Evaluation Analyses

Descriptive statistics will be provided for selected clinical laboratory test results (hematology and chemistry) and changes from baseline by scheduled time of evaluation, including the end of study visit, maximum post-treatment value, and minimum post-treatment value.

Abnormal laboratory results will be graded according to the NCI-CTCAE Version 4.0, if applicable. A shift table, presenting the 2-way frequency tabulation for baseline and the worst post-treatment value according to the NCI-CTCAE grade, will be provided for selected clinical laboratory tests. Abnormal clinical laboratory test results that are deemed as clinically significant or evaluated as Grade 3 or 4 will be listed.

11.4.3.3. Vital Sign Analyses

Descriptive statistics will be provided for the vital signs measurements and changes from baseline by scheduled time of evaluation, including the end of study visit and the maximum and minimum post-treatment values.

11.4.3.4. Electrocardiogram Analyses

All ECG parameters, including the QTc, will be listed for each subject and summarized by dose level and scheduled time of evaluation. Change from baseline will also be summarized. Relationship between dose level and QTc changes will be explored by graphs. The QTc will be calculated using Fridericia's formula.

11.4.3.5. Physical Examination Analyses

Physical examination findings including ECOG PS will be listed.

11.4.3.6. Exploratory Safety Analyses

The ECHO/MUGA findings will be listed.

11.4.4. Other Analysis

Results for pharmacogenomics analysis will be listed.

11.5. Interim Analyses

Not applicable.

11.6. Sample Size Determination

The study consists of 2 dose levels with at least 3 DLT-evaluable subjects per dose level. At least 9 DLT-evaluable subjects are needed to reach an accurate estimate of the MTD/RP2D. The sample size for extension part will depend on how many subjects are benefiting from treatment during the study.

The sample sizes have been determined by practical considerations for the study. No formal statistical assessment has been performed.

11.7. Statistical Analysis Process

The clinical study will be analyzed by QuintilesIMS.

The statistical methodology section must reflect the planned analyses.

The SAP will provide the statistical methods and definitions for analyzing the efficacy and safety data, as well as describe the approaches to be taken for summarizing other clinical study information such as subject disposition, demographic and baseline characteristics, study drug exposure, and prior and concomitant medications. The SAP will also include a description of how missing, unused, and spurious data will be addressed.

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

12. DATA INTEGRITY AND QUALITY ASSURANCE

The investigator/investigational study 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.

12.1. Monitoring and Inspections

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

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

The study 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 study 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 may be selected for audit by representatives from the Sponsor. Inspection of study site facilities (eg, pharmacy, drug storage areas, laboratories, etc.) 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.

12.2. Data Collection

The investigator or study staff will enter the data in the eCRF in accordance with the eCRF Completion Guidelines that are provided by the Sponsor.

The eCRF completion should be kept current to enable the study monitor to review the subject's status throughout the course of the study. The eCRF will be completed, reviewed, and signed off or e-signed by the investigator after all queries have been satisfactorily resolved.

The investigator e-signs according to the study data flow.

Any clinical data entered in the eCRF will be subjected to the data management procedures and will be included in the final study datasets according to Clinical Data Interchange Standards Consortium (CDISC) standards.

12.3. Data Management

The eCRFs will be produced by QuintilesIMS. Electronic Data Capture (EDC) will be used for this study, meaning that all eCRF data will be entered in electronic forms at the study site. Data collection will be completed by authorized study site staff designated by the investigator. Appropriate training and security measures will be completed with the investigator and all authorized study site staff prior to the study being initiated and any data being entered into the system for any study subjects.

All data must be entered in English. The eCRFs should always reflect the latest observations for the subjects participating in the study. Therefore, the eCRFs are to be completed as soon as possible during or after the subject's visit. To avoid interobserver variability, every effort should be made to ensure that the same individual who made the initial baseline determinations completes all safety evaluations. The investigator must verify that all data entries in the eCRFs are accurate. If some assessments are not done, or if certain information is not available or not applicable or unknown, the investigator should indicate this in the eCRF. The investigator will be required to electronically sign off on the clinical data.

The study monitor will review the eCRFs and evaluate them for completeness and consistency. The eCRF will be compared with the source documents to ensure that there are no discrepancies between critical data. All entries, corrections and alterations are to be made by the responsible investigator or his/her designee. The study monitor cannot enter data in the eCRFs. Once clinical data of the eCRF have been submitted to the central server, corrections to the data fields will be audit trailed, meaning that the reason for change, the name of the person who performed the change, together with time and date will be logged. Roles and rights of the study site staff responsible for entering the clinical data into the eCRF will be determined in advance. If additional corrections are needed, the responsible study monitor or data manager will raise a query in the EDC application. The appropriate study site staff will answer the queries sent to the investigator. This will be audit trailed by the EDC application, meaning that the name of study site staff, time, and date stamp are captured.

The eCRF is essentially considered a data entry form and should not constitute the original (or source) medical records unless otherwise specified. Source documents are all documents used by the investigator or hospital that relate to the subject's medical history, verify the existence of the subject, the inclusion and exclusion criteria, and all records covering the subject's participation in the study. They include laboratory notes, ECG results, memoranda, pharmacy dispensing records, subject files, etc.

The investigator is responsible for maintaining source documents. These will be made available for inspection by the study monitor at each monitoring visit. The investigator must submit a completed eCRF for each subject who receives study drug, regardless of duration. All supportive documentation submitted with the eCRF, such as laboratory or hospital records, should be clearly identified with the study and subject number. Any

personal information, including subject name, should be removed or rendered illegible to preserve individual confidentiality.

Electronic case report form records will be automatically appended with the identification of the creator, by means of their unique UserID. Specified records will be electronically signed by the investigator to document his/her review of the data and acknowledgement that the data are accurate. This will be facilitated by means of the investigator's unique UserID and password; date and time stamps will be added automatically at the time of electronic signature. If an entry on an eCRF requires change, the correction should be made in accordance with the relevant software procedures. All changes will be fully recorded in a protected audit trail, and a reason for the change will be required.

All AEs will be coded using the current version of the Medical Dictionary for Regulatory Activities. Concomitant medications plus prior cancer therapy will be coded using the World Health Organization Drug Dictionary.

Refer to Appendix 17.2 for details of the EDC system used for completing eCRF.

12.4. Study Documentation and Storage

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

Records of subjects, source documents, monitoring visit logs, data correction forms, eCRFs, inventory of study drug, regulatory documents (eg, protocol and amendments, IRB correspondence and approvals, approved and signed ICFs, investigator's Agreement, clinical supplies receipts, distribution and return records), and other Sponsor correspondence pertaining to the study must be kept in appropriate study files at the study site (Trial Master File). Source documents include all recordings and observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical study. These records will be retained in a secure file for the period required by the institution or study site policy. Prior to transfer or destruction of these records, the Sponsor must be notified in writing and be given the opportunity to further store such records.

12.5. Record Keeping

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

- Subject files containing completed eCRFs, ICFs, and supporting copies of source documentation (if kept)
- Study files containing the protocol with all amendments, IB, copies of relevant essential documents required prior to commencing a clinical study, and all correspondence to and from the IRB and the Sponsor

- Records related to the study drug(s) including acknowledgment of receipt at study site, accountability records, and final reconciliation and applicable correspondence

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

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

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

13. FINANCING AND INSURANCE

13.1. Finances

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

13.2. 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.

14. 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 year 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 Daiichi Sankyo has had the opportunity to review and comment on the study site's proposed publication prior to the submission for publication with the prior advice of Daiichi Sankyo Legal Affairs (intellectual property council) and with proper regard to the protection of subjects' identities.

15. ETHICS AND STUDY ADMINISTRATIVE INFORMATION

15.1. Compliance Statement, Ethics and Regulatory Compliance

This study will be conducted in compliance with the protocol, the ethical principles that have their origin in the Declaration of Helsinki, the ICH consolidated Guideline E6 for GCP (CPMP/ICH/135/95), and applicable local regulatory requirements.

15.2. Subject Confidentiality

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

The investigator must ensure that the subject's anonymity is maintained. On the eCRFs or other documents submitted to the Sponsor or QuintilesIMS, subjects should be identified by a unique subject identifier as designated by the Sponsor. Documents that are not for submission to the Sponsor or QuintilesIMS (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 the institution authorized representatives of the company, the regulatory agency(s), and the IRB have 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.

15.3. 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, before any protocol-specific procedures or any study drugs are administered. Subjects should be given the opportunity to ask questions to 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, adhere to GCP and to the ethical principles that have their origin in the Declaration of Helsinki. The consent form and any revision(s) should be approved by the IRB prior to being provided to potential subjects.

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

If the subject cannot read, then according to ICH GCP Guidelines, 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.

15.4. Regulatory Compliance

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

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

The investigator and/or Sponsor must submit and, where necessary, obtain approval from the IRB for all subsequent protocol amendments and changes to the ICF. The investigator should notify the IRB of deviations from the protocol or SAEs occurring at the study site and other AE reports received from the Sponsor or QuintilesIMS, 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, and that implementation of changes to the initial protocol and other relevant study documents happen only after the approval by the relevant regulatory bodies.

In the event of any prohibition or restriction imposed (eg, clinical hold) by an applicable Regulatory Authorities in any area of the world, or if the investigator is aware of any new information that might influence the evaluation of the benefits and risks of the study 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 noncompliance that the investigator becomes aware of.

15.5. Protocol Deviations

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

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

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

If a subject was ineligible or received an incorrect dose or study drug, 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.

15.6. 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, 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 influence the subject's willingness to continue participation in the study. The communication should be documented on medical records, for example, and it should be confirmed whether the subject is willing to remain in the study.

If the subject information is revised, it must be re-approved by the IRB. The investigator should obtain written informed consent to continue participation with the revised written information even if the 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.

15.7. Protocol Amendments

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

A global protocol amendment will affect study conduct at study site. Such amendments will be incorporated into a revised protocol document. Changes made by such 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 local protocol amendment will affect study conduct at particular study site(s) and/or in a particular region/country. Sponsor approval of local amendments will be clearly documented.

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

15.8. Study Termination

The study may be terminated at any time by the IRB, the Sponsor, or regulatory agencies as part of their duties is to ensure that the research subjects are protected.

The Sponsor reserves the right to temporarily suspend or prematurely discontinue this study at study site at any time for reasons including, but not limited to, safety or ethical issues or severe noncompliance. If the Sponsor determines such action is needed, the Sponsor will discuss this with the investigator (including the reasons for taking such action) at that time. When feasible, the Sponsor will provide prior notification to the investigator of the impending action prior to its taking effect.

The Sponsor will promptly inform all other investigators and/or study sites conducting the study if the study is suspended or terminated for safety reasons, and will also inform the regulatory authorities of the suspension or termination of the study and the reasons for the action. If required by applicable regulations, the investigator must inform the IRB promptly and provide the reasons for the suspension or termination.

If the study is prematurely discontinued, all study data must be returned to the Sponsor. In addition, arrangements will be made for return of all unused study drug in accordance with the Sponsor's applicable procedures for the study.

Financial compensation to the investigators and/or institutions will be in accordance with the agreement established between the investigator and the Sponsor.

15.9. Safety Monitoring Committee

An SMC will be established for the purpose of assessing safety and tolerability of the subjects. The SMC meetings will be held between cohorts after certain number of the enrolled subjects in 1 cohort have completed the first cycle of treatment. Ad hoc meetings will be held to discuss subject safety and DLT determination as needed.

The SMC will evaluate progress of the study, assess safety and other relevant information, and then make decisions on cohort escalations or de-escalation as well as study continuation or discontinuation. The SMC members may include medical experts of Daiichi Sankyo, study monitor of this study, and investigator of the study site. Detailed procedures of the SMC will be specified in the SMC Charter.

15.10. Address List

Please refer to Appendix 17.4 for the address list of various stakeholders involved in this study.

16. REFERENCES

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17. APPENDICES

17.1. Schedule of Events

Procedure	Screening	C1 D1	C1 D2	C1 D8	C1 D15	C1 D22	C2 D1	C2 D8	C2 D15	C2 D22	C3 D1	C3 D8	C3 D15	C4 D1	C4 D15	C5+ D1[m]	Treatment visit during the extension part		End of Treat-ment	Follow-up	PGx[o]
	≤ 28 d to - 1	WK 1	WK 1	WK 2	WK 3	WK 4	WK 5	WK 6	WK 7	WK 8	WK 9	WK 10	WK 11	WK 13	WK 15	WK 17+	Every 4 weeks ± 7 d	Every 12 weeks ± 7 d	DC + 3 d	28 ± 7 d after last dose	
Pexidartinib administration		BID (morning and evening)																			
Informed consent	X																				
Dispensing of study drug		X					X				X			X		X	X	X			
Dispensing of subject diary		X					X				X			X		X	X	X			
Demography and medical history	X																				
Height[a], weight	X																		X		
ECOG PS	X						X				X			X		X			X		
Pulse, BP, RR, temperature[b]	≤ 7 d	X		X	X	X	X		X		X			X		X		X	X		
Physical examination[b]	≤ 7 d	X		X	X	X	X		X		X			X		X		X	X		
ECG[c]	≤ 7 d	X					X				X			X		X		X	X		
ECHO/MUGA	≤ 21 d						X											X	X		
Chemistry, hematology[d]	≤ 7 d	X		X	X	X	X		X		X			X		X	X	X	X		
Liver function tests[d,e]	≤ 7 d	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Urinalysis[d]	≤ 7 d	X		X	X	X	X		X		X			X		X		X	X		
Coagulation tests[d]	≤ 7 d	X															X	X	X		

Procedure	Screening	C1 D1	C1 D2	C1 D8	C1 D15	C1 D22	C2 D1	C2 D8	C2 D15	C2 D22	C3 D1	C3 D8	C3 D15	C4 D1	C4 D15	C5+ D1[m]	Treatment visit during the extension part		End of Treat-ment	Follow-up	PGx[o]
	≤ 28 d to - 1	WK 1	WK 1	WK 2	WK 3	WK 4	WK 5	WK 6	WK 7	WK 8	WK 9	WK 10	WK 11	WK 13	WK 15	WK 17+	Every 4 weeks ± 7 d	Every 12 weeks ± 7 d	DC + 3 d	28 ± 7 d after last dose	
Pexidartinib administration		BID (morning and evening)																			
Hormone testing[f]	≤ 7 d						X		X										X		
CT/MRI of tumor[g]	≤ 21 d										X					X (at least every 3 cycles)		X	X		
Serum pregnancy test[h]	≤ 14 d																	X	X		
PK, blood sampling[i]		X	X	X	X	X	X														
PD, blood sampling[j]		X			X		X														
Concomitant medications[k]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	
Adverse events[l]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
PGx informed consent																					X
PGx blood sampling[n]																					X

BID = twice daily; BP = blood pressure; C = cycle; CT = computed tomography; D(d) = day; DC: Date of discontinuation (The date of discontinuation of treatment is defined as the date of decision by the investigator); ECG = electrocardiogram; ECHO = echocardiogram; ECOG PS = Eastern Cooperative Oncology Group Scale of Performance Status; MRI = magnetic resonance imaging; MUGA = multi-gated acquisition; PD = pharmacodynamic; PK = pharmacokinetic; RR = respiratory rate; WK = week, PGx = pharmacogenomics.

a Height (only at screening) will be recorded.

b Physical examination including vital signs (systolic and diastolic blood pressure, pulse rate, respiratory rate, and body temperature) will be done on visit days indicated by an X.

c 12-Lead ECG will be performed in triplicate. Readings will be performed predose on Day 1 of each cycle and at the end of treatment.

d Safety laboratory samples for Day 1 predose (complete blood count with differential and reticulocyte counts, serum chemistry, urinalysis, and coagulation profile) can be collected within 72 h before the first dose.

e Alkaline phosphatase, total and direct bilirubin, ALT, AST, and GGT should be assessed at screening, weekly for 10 weeks (C1D1 through C3D15), and then biweekly till C5D1 (C4D1, C4D15, and C5D1) and on Day 1 of every cycle thereafter.

f Women who are not using hormonal contraception will be tested for levels of FSH, LH, progesterone, and estradiol. Hormone testing will not be required for women who have either had an oophorectomy or are postmenopausal. Men will be tested for levels of LH, FSH, and testosterone. Male subjects whose testosterone level is below baseline at the last assessment should be followed until the level has been stabilized or returned to baseline.

g Tumor assessment by physical examination and RECIST v1.1 will be performed at the screening period and at least every 2 cycles (± 7 days) in the first 4 cycles after C1D1 and thereafter at least every 3 cycles (± 7 days) if the subject remains in the study therapy, and the end of treatment.

h Women of childbearing potential must have a serum pregnancy test within 14 days of randomization (or, where different regulations apply, within 72 h of randomization). Women who have documentation of at least 12 months of spontaneous amenorrhea and have an FSH level > 40 mIU/mL will be considered postmenopausal and need not undergo pregnancy testing.

i On C1D1 and C1D15, blood will be obtained at predose and 0.5, 1, 2, 4 and 8 hours after morning dose. In addition, blood will be collected at predose on C1D2, C1D8, C1D22, and C2D1.

j The PD sample (for plasma CSF-1 and adiponectin) will be obtained at predose, and predose on C1D1, C1D15, and C2D1.

k Subjects receiving concomitant warfarin should have their anticoagulation status carefully monitored for any necessary dose adjustments.

l SAEs are monitored upon occurrence during extension part. AEs will be reported at treatment visits.

m Subjects will continue study visit in dose escalation part till the cut-off date (The cut-off is defined as the date after all subjects have either discontinued the study or completed at least 4 cycles. Subjects who are still ongoing in the study after the cut-off date and who are responding or stable after pexidartinib during the dose escalation part will enter extension part to receive extended treatment of pexidartinib.

n The pharmacogenomic blood sample is optional. If taken, it should only be taken once as soon as reasonably possible after the subject has signed the consent form.

o The pharmacogenomic sample visit. The pharmacogenomic blood sample could be collected anytime during study conduction.

17.2. Electronic Data Capture System

The EDC system used for completing eCRF in this study is shown below.

Name of EDC system used for completing the eCRF	Medidata Rave®
EDC system developer	Medidata Solutions Inc.
Entry method	Web-based data entry
Input terminal	Desktop/laptop computer at the study site

Abbreviations: eCRF = electronic case report form; EDC = electronic data capture.

17.3. CYP3A4 Inhibitors and Inducers

Strong Inhibitors	Strong Inducers
Protease inhibitors • Ritonavir • Indinavir • Nelfinavir Macrolide antibiotics • Erythromycin • Telithromycin • Clarithromycin Azole antifungals • Fluconazole • Ketoconazole • Itraconazole Chloramphenicol (antibiotic) Nefazodone (antidepressant) Bergamottin (constituent of grape fruit juice) Aprepitant (antiemetic) Verapamil (calcium channel blocker)	Anticonvulsants, mood stabilizers • Phenytoin • Carbamazepine • Oxcarbazepine Non-nucleoside reverse transcriptase inhibitors • Efavirenz • Nevirapine • Etravirine Phenobarbital (barbiturate) Rifampicin (bactericidal) Modafinil (stimulant) Hyperforin (constituent of St. John's wort) Cyproterone (antiandrogen, progestin)

Source: Flockhart, DA. Drug Interactions: Cytochrome P450 Drug Interaction Table. Indiana University School of Medicine [2009]. Available from: http://medicine.iupui.edu/clinpharm/ddis/main-table/. Accessed October 22, 2014.

17.4. Address List

Refer to protocol supplement Version 3.0 dated 10 APR 2018.