CLINICAL STUDY PROTOCOL

AN OPEN-LABEL, SINGLE SEQUENCE, CROSSOVER STUDY ASSESSING THE EFFECT OF PEXIDARTINIB ON THE PHARMACOKINETICS OF MIDAZOLAM AND S-WARFARIN IN PATIENTS

PL3397-A-U126

IND 105521

VERSION 1.0, 28 APRIL 2017

DAIICHI SANKYO INC.
211 MT AIRY ROAD
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INVESTIGATOR AGREEMENT

AN OPEN-LABEL, SINGLE SEQUENCE, CROSSOVER STUDY ASSESSING THE EFFECT OF PEXIDARTINIB ON THE PHARMACOKINETICS OF MIDAZOLAM AND S-WARFARIN IN PATIENTS

Sponsor Approval:

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

[redacted] [redacted]

Print Name **Signature**

Clinical Study Leader 30 Apr 2017

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 patient 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 (ICH) 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 patients' 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.

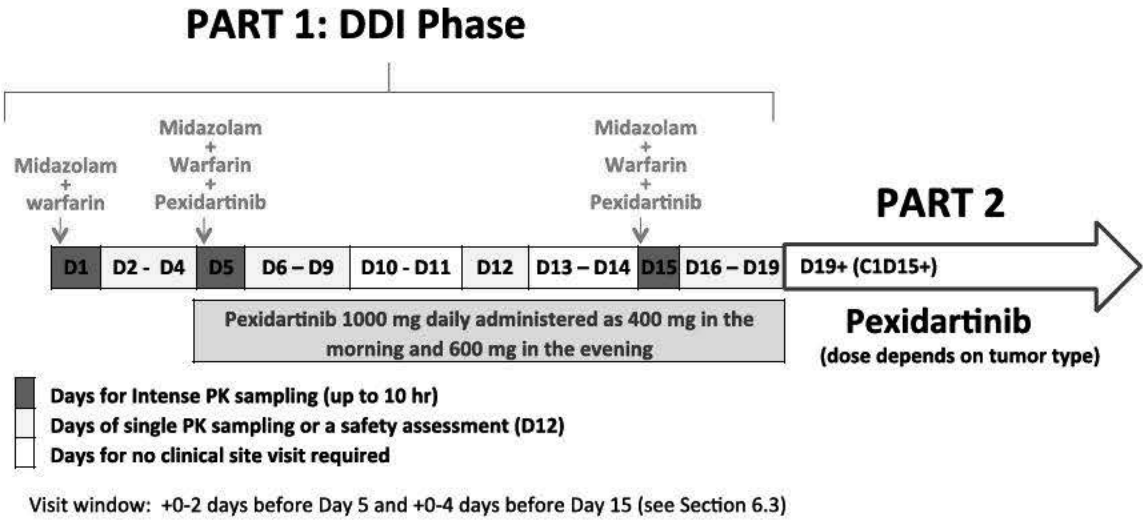
I understand that the Sponsor may decide to suspend or prematurely terminate the study at any time for whatever reason; such a decision will be communicated to me in writing. Conversely, should I decide to withdraw from execution of the study, I will communicate my intention immediately in writing to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

Print Name	**Signature**
Title	**Date (DD MMM YYYY)**

PROTOCOL SYNOPSIS

IND Number:	105521
EudraCT:	2017-001687-38
Protocol Number:	PL3397-A-U126
Investigational Product:	PLX3397
Active Ingredient/INN:	Pexidartinib
Study Title:	An open-label, single sequence, crossover study assessing the effect of pexidartinib on the pharmacokinetics of midazolam and S-warfarin in patients
Study Phase:	Phase 1, drug-drug interaction (DDI) study
Indication Under Investigation:	Pexidartinib DDI with midazolam and S-warfarin Safety and efficacy will also be evaluated in various tumors.
Study Objectives:	Primary Objective: • To assess the effects of pexidartinib on the pharmacokinetic (PK) parameters of single-dose midazolam and S-warfarin in patients Secondary Objectives: • To determine the overall response rate (ORR) in patients with tenosynovial giant cell tumor (TGCT), kit-mutant melanoma, kit-mutant gastrointestinal stromal tumor (GIST), or other tumors • To assess the safety and tolerability of pexidartinib alone and in combination with single-dose midazolam and S-warfarin • To determine the safety of pexidartinib given as monotherapy over longer periods • To evaluate the PK of pexidartinib and ZAAD-1006a

Study Schema:



Study Design:

This open-label, single sequence, crossover study will comprise 2 parts:

Part 1: An initial single sequence crossover part to evaluate the effect of pexidartinib on the PK of midazolam and S-warfarin, the DDI Phase.

Part 2: An evaluation of efficacy and safety of pexidartinib treatment in various tumors.

Screening will take place between Day -21 and Day -1. The total duration of participation (excluding Screening) for each patient in Part 1 will be approximately 18 d. Pexidartinib treatment (1000 mg/d) will commence on Day 5. Thereafter, pexidartinib treatment will continue BID into Part 2 of the study at the doses defined below to evaluate efficacy and safety until there is no longer clinical benefit or until other reasons for discontinuation are met.

Part 1:

- On Day 1 patients will receive the single oral dose of midazolam (2 mg) and S-warfarin (10 mg with vitamin K [5 mg]), and PK samples will be collected over approximately 48 h and 96 h, respectively.
- On Day 5 pexidartinib (1000 mg/d) in twice daily (BID) dosing will be initiated and continue throughout the remainder of Part 1 and into Part 2. On the first day of pexidartinib treatment (Day 5), a single dose of midazolam (2 mg) and S-warfarin (10 mg with vitamin K [5 mg]) will be co-administered with the morning pexidartinib dose

	(400 mg), and PK samples will be collected over 10 h (pexidartinib), 48 h (midazolam), or 96 h (S-warfarin). • On Day 15, a single dose of midazolam (2 mg) and S-warfarin (10 mg with vitamin K [5 mg]) will be co-administered with the morning dose of pexidartinib (400 mg), and PK samples will be collected over 10 h (pexidartinib), 48 h (midazolam), or 96 h (S-warfarin). In Part 2, patients will continue to receive pexidartinib BID at a dose of 800 mg/d or 1000 mg/d depending upon the tumor type as defined in the protocol. Patients will be assessed for safety and efficacy. An optional tumor biopsy or archival tumor specimen under specific informed consent and/or blood samples for circulating tumor DNA may be collected at Screening and during pexidartinib treatment for exploratory analysis of tumor biomarkers at the discretion of the Investigator/patient.
Study Duration:	Patients will be screened no longer than 21 d prior to dosing on Day 1. The duration of Part 1 of the study will be approximately 18 d for each patient. Part 2 of the study will continue until there is no longer clinical benefit or until other reasons for discontinuation are met. First patient enrolled: approximately Q2 2017 Last patient last visit for primary DDI objective phase: approximately Q4 2017 Last patient last visit overall: approximately Q3 2018
Study Sites and Location:	Approximately 12 sites in Australia, South Korea, New Zealand, Taiwan, US, EU, and other countries.
Patient Eligibility Criteria:	Inclusion Criteria: Patients must meet the following inclusion criteria to be enrolled in the study: 1. Age ≥ 18 y or ≥ the legal age for being considered as an adult in the country where the patient is screened at the time of signing informed consent. 2. A diagnosis of TGCT, kit-mutant melanoma, kit-mutant GIST, leukemia, or other tumor for which there is no other standard systemic therapy. Patients with TGCT or other non-malignant tumor must be approved by the Sponsor prior to Screening and enrollment. Prior pexidartinib is permitted for TGCT patients unless

ineffective or not tolerated and there has been a washout period of at least 4 wk.

3. Women of childbearing potential must have a negative serum pregnancy test within 14 d prior to enrollment. (Where demanded by local regulations, this test may be required within 72 h prior to enrollment).
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, respectively, by using a highly effective contraception method, as described below, throughout the study and up to 90 d after completion. Highly effective methods of contraception include intra-uterine device (nonhormonal or hormonal); bilateral tubal occlusion; vasectomy; sexual abstinence (only if this is in line with the patient's current lifestyle); or barrier methods (eg, condom, diaphragm) used in combination with hormonal methods associated with inhibition of ovulation. Women of nonchildbearing potential may be included if they are either surgically sterile or have been postmenopausal for ≥ 1 y. Women who have documentation of at least 12 mo of spontaneous amenorrhea and have a follicle-stimulating hormone level > 40 mIU/mL will be considered postmenopausal.
5. Adequate hematologic, hepatic, and renal function, defined by:
    - Absolute neutrophil count ≥ 1.5×10^9/L.
    - Hemoglobin > 10 g/dL.
    - Platelet count ≥ 100×10^9/L.
    - Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 1.5 × upper limit of normal (ULN).
    - Total bilirubin (TBil) ≤ ULN with an exception of patients with confirmed Gilbert's syndrome. For patients with confirmed Gilbert's syndrome, the total bilirubin should be ≤ 1.5 × ULN.
    - Serum creatinine ≤ 1.5 × ULN.
6. Willingness and ability to use a pill diary.

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

Exclusion Criteria:

Patients must not meet the following exclusion criteria to be enrolled in the study:

1. Known active or chronic human immunodeficiency virus (HIV) or hepatitis C virus (HCV) infection, or positive hepatitis B (HepB) surface antigen.
2. Known active tuberculosis.
3. Hepatobiliary diseases including biliary tract diseases, autoimmune hepatitis, inflammation, fibrosis, cirrhosis of liver caused by viral, alcohol, or genetic reasons. Gilbert's disease is allowed if TBil is $\leq 1.5 \times$ ULN.
4. Women who are breastfeeding.
5. Patients with poor metabolizer status of Cytochrome P450 (CYP) 2C9.
6. Patients on potent CYP2C9, CYP3A4, and Uridine 5'-diphospho-glucuronosyltransferase family 1 member A4 (UGT1A4) inducer and inhibitors and potent P-glycoprotein (P-gp) inhibitors and inducers, unless these medications are discontinued at least 14 d before study drug administration. Foods or beverages containing CYP3A4/5 inhibitors (eg, grapefruit, pomegranate, pomelo, and star fruit) should be avoided throughout the study.
7. A screening Fridericia-corrected QT (QTcF) interval $\geq$ 450 ms (men) or $\geq$ 470 ms (women).
8. History of hypersensitivity to any investigational products, including their excipients.
9. Inability to swallow capsules.
10. Inability to complete study procedures.

Dosage Form, Dose and Route of Administration:	• Pexidartinib will be administered orally at a total daily dose of 1000 mg administered as a split dose of 400 mg (am) and 600 mg (pm) given continuously in 28-d cycles. The dose of pexidartinib for patients with TGCT or other non-malignant tumor will be reduced to 800 mg/d (400 mg BID) after 14 d of treatment (after completion of Part 1). The dose of pexidartinib will

	be modified depending upon tolerance as defined in the protocol. • Midazolam will be administered as a single oral dose of 2 mg. • S-warfarin will be administered as a single oral dose of 10 mg with vitamin K (5 mg).
Study Treatment Administration Time and Duration:	• S-warfarin reference treatment: single oral dose of S-warfarin (10 mg) on Day 1 with vitamin K (5 mg). • Midazolam reference treatment: single oral dose of midazolam (2 mg) on Day 1. • S-warfarin test treatment: single oral dose of warfarin (10 mg) with vitamin K (5 mg) on Day 5 concomitantly with pexidartinib and on Day 15 following approximately 10 d of pexidartinib BID dosing. • Midazolam test treatment: single oral dose of midazolam (2 mg) on Day 5 concomitantly with pexidartinib and on Day 15 following approximately 10 d of pexidartinib BID dosing. • Pexidartinib treatment: Pexidartinib will be administered orally as a total daily dose of 1000 mg administered as split dose of 400 mg (am) and 600 mg (pm) continuously in 28-d cycles starting from Day 5. The dose of pexidartinib for patients with TGCT or other non-malignant tumor will be reduced to 800 mg/d (400 mg BID) after 14 d of treatment (after completion of Part 1). The dose of pexidartinib will be modified depending upon tolerance as defined in the protocol.
PK sampling Time Points:	• Plasma samples for midazolam will be collected at predose, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 24, and 48 h (±10 min up to 1 h, ±10% thereafter) on Days 1 to 3 and also when co-administered with pexidartinib on Days 5 to 7 and Days 15 to 17. • Plasma samples for S-warfarin will be collected at predose, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10 (±1), 24 (±2), 48 (±2), 72 (±2), and 96 (±2) h on Days 1 to 5 and also when co-administered with pexidartinib on Days 5 to 9 and Days 15 to 19.

	• Plasma samples for pexidartinib and its metabolites will be collected at predose, 0.5, 1, 2, 3, 4, 6, 8, and 10 (±1) h after the first dose on Day 5 and at steady state when co-administered with midazolam and S-warfarin on Day 15.
Efficacy Assessments:	Efficacy will be assessed by magnetic resonance imaging, computerized tomography scan, or other method appropriate to the type of tumor and read locally. Assessments will be performed during Screening and ±7 d after the end of every two 28-d treatment cycles, or other frequency appropriate to the tumor type, starting with the first dose of pexidartinib in Part 1.
Safety Assessments:	• A physical examination will be performed at Screening, at subsequent times as defined in the schedule of events, and at the end of treatment. • Serum chemistry, hematology, and urinalysis will be obtained at Screening, at subsequent times as defined in the schedule of events, and at the end of treatment. • Liver function tests as part of serum chemistry will be conducted on an at least weekly basis for the first 8 wk of pexidartinib treatment starting from the first dose in Part 1 (Day 5). After Week 8, the frequency of liver function tests will be reduced to once every 2 wk through Cycle 3, followed by monthly. If any abnormality is detected in the liver function tests, then follow-up laboratory tests will be performed on a weekly basis. The frequency of follow-up liver function tests will be increased to twice weekly for all Grade 3 aminotransferase increases and for any grade aminotransferase increase associated with bilirubin increase. (No bilirubin increase is defined as any 1 or more of the following: TBil ≤ ULN, TBil < 20% above baseline, or direct bilirubin < ULN). • Vital signs and 12-lead electrocardiograms (ECGs) will be performed at Screening, at subsequent times as defined in the schedule of events, and at the end of treatment.

	• A blood sample (10 mL) for pharmacogenomic analysis will be collected from each patient at Screening. • Adverse events and concomitant medications will be evaluated throughout the study starting from the time of informed consent.
Other Assessments:	Optional tumor biopsy samples or archival tumor specimen under specific informed consent or blood samples for circulating tumor DNA may be collected at Screening and during pexidartinib treatment at the discretion of the Investigator/patient.
Planned Sample Size:	Approximately 30 patients will be enrolled to achieve 24 patients evaluable for DDI.
PK Parameters:	• Plasma concentration-time data will be analyzed using noncompartmental methods. The following PK parameters of midazolam and S-warfarin will be calculated: Cmax, tmax, and AUClast. If data permits, other PK parameters including t1/2 and AUCinf will be reported for midazolam and S-warfarin. • Plasma PK parameters (Cmax, tmax, and AUClast) will be calculated for pexidartinib and its primary metabolite, ZAAD-1006a after the first dose and multiple doses.
Key Efficacy Parameters:	• Best objective response per Response Evaluation Criteria in Solid Tumors, version 1.1 (RECIST 1.1) • Duration of response • Time to progression (for TGCT and other non-malignant tumors) • Progression-free survival (for malignant tumors)
Safety Parameters:	• Treatment emergent adverse events • Vital signs • 12-lead ECGs • Clinical laboratory tests including AST/ALT/TBil
PK Analysis:	Individual plasma concentration-time data and descriptive summary statistics will be listed, tabulated, and presented graphically by treatment and visit. Pharmacokinetic parameters

	for midazolam, 5-hydroxy midazolam, S-warfarin, and pexidartinib and ZAAD-1006a will be summarized using descriptive statistics and graphically (Cmax and AUC). An analysis of variance (ANOVA) model with treatment as fixed effects, and patient as random effect will be used to compare natural-log transformed PK parameters (Cmax and AUClast) of the substrates with and without the co-administration of pexidartinib. The combination treatments (pexidartinib + substrate) will be the test and substrate alone will be the reference for the comparison in regards to each substrate. Geometric mean ratios and their corresponding 90% confidence intervals (CI) between the treatments will be calculated by anti-log transformation. Time to reach maximum plasma concentration will be analyzed using a nonparametric method. The point estimate of the treatment difference and the corresponding 95% confidence intervals will be calculated and anti-logged to obtain the point estimate and 95% CI on the linear scale for the ratio of geometric means of the test as compared with the reference. No DDI will be concluded if the 90% CI of the ratio of the test to the reference completely remains within 80-125%.
Statistical Analyses:	Safety and efficacy will be summarized using descriptive statistics.
Sponsor:	Daiichi Sankyo Inc. 211 Mt Airy Road Basking Ridge, NJ 07920-2311, USA (Sponsor in a specific country will be the regional Daiichi Sankyo clinical research office.)

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

ABBREVIATION	DEFINITION
AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC	Area under the plasma concentration-time curve
AUCinf	Area under the plasma concentration-time curve up to infinity
AUClast	Area under the plasma concentration-time curve up to the last measurable time
BID	Twice daily
C#D#	Cycle # Day #
CI	Confidence interval
Cmax	Maximum Plasma Concentration
CR	Complete response
CRO	Contract Research Organization
CSF1	Colony-stimulating factor 1
CSF1R	Colony-stimulating factor 1 receptor
CTCAE	Common Terminology Criteria for Adverse Events
CYP	Cytochrome P450
DCR	Disease control rate
DDI	Drug-drug interaction
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EIU	Exposure In Utero
FAS	Full Analysis Set
FDA	Food and Drug Administration
FLT3	Fms-like tyrosine kinase 3
GCP	Good Clinical Practice
GGT	Gamma glutamyl transferase
GIST	Gastrointestinal stromal tumor
HCl	Hydrochloride
HCV	Hepatitis C virus

ABBREVIATION	DEFINITION
HepB	Hepatitis B
HIV	Human immunodeficiency virus
IB	Investigator's Brochure
IC50	Half maximal inhibitory concentration
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
INR	International normalized ratio
IRB	Institutional Review Board
ITD	Internal tandem duplications
ITT	Intent-to-treat
KIT	Receptor for stem cell factor
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic resonance imaging
NCI	National Cancer Institute
ORR	Overall response rate
OTC	Over-the-counter
PD	Progressive disease
PDy	Pharmacodynamics
P-gp	P-glycoprotein
PGx	Pharmacogenomics
PK	Pharmacokinetics
PR	Partial response
PRO	Patient-reported outcome
PT	Preferred term
QTcF	Fridericia corrected QT interval
RECIST 1.1	Response Evaluation Criteria in Solid Tumors, versions 1.1
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SAVER	Serious Adverse Event Report
SCF	Stem cell factor
SD	Stable disease

ABBREVIATION	DEFINITION
SOC	System organ class
SUSAR	Suspected unexpected serious adverse reaction
t1/2	Terminal elimination half-life
TBil	Total bilirubin
TEAE	Treatment-emergent adverse event
TGCT	Tenosynovial giant cell tumor
Tmax	Time to Reach Maximum Plasma Concentration
ULN	Upper limit of normal

1. INTRODUCTION

1.1. Scientific Background – Pexidartinib (PLX3397)

Pexidartinib is a novel orally active small-molecule tyrosine kinase inhibitor that targets Colony-stimulating factor 1 (CSF1) receptor (CSF1R), KIT (the receptor for stem cell factor), and oncogenic fms-like tyrosine kinase 3 (FLT3), the receptor for FLT3 ligand. When screened in vitro against a broad panel of 226 kinases, pexidartinib showed potent and selective inhibition against its intended targets: CSF1R, KIT, and activated FLT3. Pexidartinib also blocked osteoclast differentiation and cell growth of CSF1-dependent cell lines. Pexidartinib blocks CSF1R activity in a variety of in vivo models. Pexidartinib shows dose-dependent inhibition of splenomegaly in an engineered CSF1R-dependent mouse model. In the collagen-induced arthritis model, pexidartinib shows substantial efficacy by blocking the activity of macrophages and osteoclasts that infiltrate the diseased joints, reduces synovial inflammation and cartilage destruction, and reduces clinical scores for joint and digit swelling and redness even with treatment of advanced disease.

The effects of pexidartinib on multiple aspects of tumorigenesis have been characterized in cellular and in vivo assays. The proliferation of cell lines that depend on CSF1, stem cell factor (SCF), or endogenous FLT3- internal tandem duplications (ITD) is inhibited at half maximal inhibitory concentration (IC50) values below 1 μmol/L. Furthermore, CSF1-induced autophosphorylation of CSF1R and SCF-induced autophosphorylation of KIT are potently inhibited by pexidartinib. Finally, the receptor activator of NF-kappa B ligand (RANK-L)- and CSF-1-dependent differentiation of osteoclast precursors is also potently inhibited by pexidartinib. These in vitro results translate to pexidartinib effects in a variety of in vivo models for CSF1R-dependent proliferation, CSF1R-dependent osteoclast differentiation, FLT3-ITD-dependent tumor growth, and KIT-dependent mast cell proliferation.

Additional detailed information regarding the nonclinical pharmacology and toxicology of pexidartinib can be found in the Investigator's Brochure (IB).[1]

1.2. Clinical Experience

1.2.1. Clinical Safety

Across the clinical program, the most frequent treatment-emergent adverse events (TEAEs) (≥20%) among all treated patients included fatigue, nausea, decreased appetite, diarrhea, vomiting, anemia, constipation, hair color changes (depigmentation), headache, and increased aspartate transaminase (AST). Severe skin reactions including erythema multiforme and drug reaction with eosinophilia and systemic symptoms have been observed in the clinical studies, though a relationship to pexidartinib has not been established. In addition acute febrile neutrophilic dermatosis has been observed in acute myeloid leukemia subjects.

In uncontrolled clinical studies of single agent pexidartinib and in combination with other anti-cancer agents, bone marrow suppression with leukopenia (neutropenia and/or lymphopenia), anemia and thrombocytopenia, either alone or with pancytopenia, has

been observed. If clinically significant reduction of neutrophils, serum hemoglobin, or platelets counts is observed, the patient should be monitored closely and protocol-defined dose modification should be followed. Standard of care supportive measures should be initiated, including broad spectrum antibiotics, or hematopoietic growth factors, as appropriate.

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 wk, have generally resolved with treatment discontinuation, but in some cases have been severe, requiring liver dialysis and had a protracted course (> 5 mo).

Further details on the clinical and preclinical safety with pexidartinib is provided in the IB.[1]

1.2.2. Tenosynovial Giant Cell Tumor

Tenosynovial giant cell tumor (TGCT) is a group of neoplasms including pigmented villonodular synovitis and giant cell tumor of the tendon sheath (GCT-TS). It is a rare, usually non metastatic tumor that affects the synovium, joints, and tendon sheaths, resulting in swelling, pain, stiffness, and reduced mobility in the affected joint or limb. It is estimated that TGCT has an annual incidence of 11 cases per million.[3] Primary treatment of TGCT includes surgery to remove the tumor; however, in patients with a diffuse form where it can wrap around bone, tendons, ligaments, and other parts of the joint, the tumor is more difficult to remove and may require multiple surgeries or joint replacements, eventually advancing to the point where surgery is no longer an option and amputation may be considered. It is estimated that the rate of recurrence in the diffuse type of the disease can be 40% or higher. New, effective, nonsurgical treatment options are greatly needed for the treatment of TGCT.

Study PLX108-01 is an ongoing open-label 2-part dose-escalation study with an expansion cohort. In the initial dose escalation part of the study, patients with advanced solid tumors received pexidartinib daily at oral doses ranging from 200 mg to 1200 mg. At the conclusion of this part of the study, the identified Recommended Phase 2 Dose was 1000 mg/d administered as a split dose. The objective of the ongoing extension cohort part of PLX108-01 is to evaluate the potential antitumor activity of pexidartinib in patients with selected tumor types, including TGCT.

A total of 39 patients with TGCT were enrolled and treated with pexidartinib in this ongoing study. The first patient was enrolled on 18 Jul 2012, and the last patient was enrolled on 04 Jun 2015. Based upon the last data cut (21 Jan 2016), median treatment duration for this cohort was 379 d, and the longest duration was 1134 d (approximately 38 mo). Thirty-three subjects were treated for 6 mo or longer, 23 subjects were treated for 1 y or longer, and 7 subjects were on treatment for more than 2 y.

Of the 39 intent-to-treat (ITT) subjects, 36 were evaluable (ie, had a baseline and at least one post-baseline radiographic scan) for response by Response Evaluation Criteria in Solid Tumors, version 1.1 (RECIST 1.1) per local reading, and 20 had a confirmed partial response (PR), for an objective response rate of 51% (95% confidence interval

[CI]: 35% to 68%) and 56% (95% CI: 38% to 72%) for the ITT and evaluable populations, respectively. An additional 16 subjects had stable disease (SD), including one unconfirmed PR at the time of the analysis, for a disease control rate (DCR) (DCR = PR + SD) of 92% and 100% for the ITT and evaluable subjects, respectively. Nine subjects experienced at least 50% reduction in longest tumor diameter. Four subjects who had progressed on or after prior use of imatinib or nilotinib experienced either PR (3 subjects) or SD (1 subject). Most of the subjects who achieved a PR with pexidartinib treatment did so within the first 6 mo of treatment, and many of these subjects are continuing on treatment for more than 1 y. These results demonstrate that pexidartinib provides prolonged control of this disease.

The Phase 1 study was amended to collect patient-reported outcome (PRO) data for Brief Pain Inventory Worst Pain and Worst Stiffness. Based upon a cut-off of 31 Jul 2015, a summary of the PRO data and their correlation to tumor size changes shows that clinical benefit is observed on these PRO endpoints and the improvement is associated with reduction in tumor size change.

The most frequently reported TEAEs among subjects with TGCT were fatigue (82.1%), hair color changes (69.2%), nausea (64.1%), arthralgia (46.2%), periorbital edema (38.5%), dysgeusia (35.9%), diarrhea (33.3%), pruritus (33.3%), rash (33.3%), and headache (30.8%). The most common severe or life-threatening (Grade 3 or Grade 4) adverse events (AEs) were diarrhea (7.7%), alanine transaminase (ALT) increased (7.7%), and AST increased (7.7%). These AEs were reversible and well-managed with dose interruption or reduction. The following treatment-related severe adverse events (SAEs) were reported for the TGCT subjects in PLX108-01: hyponatremia, rash, and pruritus, with 1 subject for each. Adverse events leading to study treatment discontinuation occurred in 11 subjects. These events included cognitive change or concentration impairment (4 subjects), fatigue (2 subjects), left hand pain (1 subject), recurrent inflammatory arthritis (1 subject), diarrhea and deep vein thrombosis (1 subject), AST/ALT increase (1 subject), exacerbation of sciatica (1 subject), and exacerbation of psoriasis (1 subject).

Pexidartinib is now being evaluated in a Phase 3 clinical study for the treatment of symptomatic TGCT, where surgical resection is potentially associated with worsening functional limitation or severe morbidity. Three cases of suspected cholestatic liver injury were reported. As a result, an increased frequency of liver function monitoring and other hepatic safety risk mitigation procedures have been implemented into this study.

1.2.3. Other Tumors

Pexidartinib has been or is being evaluated in multiple clinical studies in a variety of other tumor types, including relapsed or refractory Hodgkin's lymphoma, recurrent and in newly diagnosed glioblastoma multiforme, advanced metastatic prostate cancer, and relapsed or refractory acute myeloid leukemia. Pexidartinib is also being evaluated in combination with paclitaxel and separately with pembrolizumab in advanced incurable solid tumors. These studies and the safety and efficacy results are described in detail in the IB.[1] Preclinical studies of pexidartinib in a variety of tumor models are also described.

1.3. Study Rationale

1.3.1. Rationale

This study will assess how pexidartinib affects the pharmacokinetics (PK) of midazolam (a known probe substrate of Cytochrome P450 [CYP]3A4) and S-warfarin (a known probe substrate of CYP2C9) after single and multiple doses of pexidartinib.

Based on in vitro data, pexidartinib has the potential to inhibit CYP3A4 and CYP2C9 with Ki values of 15.9 μM and 12.1 μM, respectively. Additionally, based on a physiologically based PK model, CYP3A4 and CYP2C9 are predicted to have an AUCR values of 11.9 and 2.2, respectively, which exceed FDA's cut off (1.25) for determining whether in vivo studies are needed or additional clinical evaluation is needed (FDA Guidance 2012). In vitro data indicates that pexidartinib has potential for both time-dependent inhibition and an induction potential for CYP3A4 isozyme. Therefore, in Part 1 of this study, the effect of pexidartinib on the CYP3A4 substrate midazolam will be investigated following both single and multiple doses of pexidartinib. The PK of midazolam will be evaluated upon the initial administration of pexidartinib to evaluate the direct inhibitory effects of pexidartinib on CYP3A4. Finally, the PK of midazolam will be evaluated again after multiple doses of pexidartinib administration to assess the net effect of possible induction and time-dependent inhibition of pexidartinib on CYP3A4. S-warfarin, which is the sensitive probe for CYP2C9, has a half-life of approximately 40 h. To maintain pexidartinib exposure during the elimination phase of warfarin PK, pexidartinib dosing has to be continued following a single dose of warfarin. Additionally, following multiple dosing with 1000 mg/d administered as split dose of 400 mg and 600 mg, pexidartinib exposure is approximately 2 to 3 fold the exposure after the first dose. Therefore, this multiple dose study will allow evaluation of the perpetrator potential of pexidartinib at the clinically relevant exposure.

After Part 1, the study will be continued in patients with a diagnosis of TGCT, kit-mutant melanoma, kit-mutant gastrointestinal stromal tumor (GIST), leukemia, or other tumor for which there is no other standard systemic therapy. These patients will continue to receive pexidartinib treatment to generate more information on the safety and efficacy of pexidartinib in a variety of tumors.

1.3.1.1. S-Warfarin

Warfarin is utilized in this study because it is a known probe substrate of CYP2C9. Warfarin is an anticoagulant which acts by inhibiting vitamin K-dependent coagulation factors, which include Factors II, VII, IX, and X, and the anticoagulant proteins C and S. Warfarin is thought to interfere with clotting factor synthesis by inhibition of the regeneration of vitamin K1 epoxide. The degree of depression is dependent upon the dosage administered.

Warfarin is essentially completely absorbed after oral administration with peak concentration generally attained within the first 4 hours. Warfarin distributes into a relatively small apparent volume of distribution (V/F) of about 0.14 L/kg. Approximately 99% of the drug is bound to plasma proteins. The elimination of S-warfarin is almost entirely by metabolism. Warfarin is stereo-selectively metabolized by hepatic CYP

enzymes to inactive hydroxylated metabolites. The CYP450 isozymes involved in the metabolism of S-warfarin include CYP2C9, CYP2C19, CYP2C8, CYP2C18, CYP1A2, and CYP3A4. CYP2C9 is likely to be the principal form of human liver cytochrome P450 which metabolizes S-warfarin.

The t1/2 of S-warfarin after a single dose is approximately 1 wk; however, the effective t1/2 ranges from 20 to 60 hours, with a mean of about 40 hours. The Absorption, Distribution, Metabolism, and Excretion study showed that up to 92% of the orally administered dose is recovered in urine. Very little S-warfarin is excreted unchanged in urine. Urinary excretion is in the form of metabolites.

Potential adverse reactions to warfarin may include:

- Fatal or nonfatal hemorrhage from any tissue or organ
- Bleeding
- Necrosis of skin and other tissue and
- Hypersensitivity/allergic reactions, systemic cholesterol microembolization, purple toes syndrome, hepatitis, cholestatic hepatic injury, and jaundice

Since warfarin is a known and FDA-recommended probe substrate of CYP2C9 (see FDA, C. C. [2006] Guidance for Industry: drug interaction studies-study design, data analysis, and implications for dosing and labeling) and it has been validated in previous Cooperstown 5 + 1 cocktail studies,[2] it has been selected in the current study as a probe drug to test the effect of single and multiple doses of pexidartinib on the PK of drugs metabolized by CYP2C9.

In the current study design, vitamin K will be dosed with warfarin at the same time to prevent the pharmacodynamic effects of warfarin without altering the stereoisomer PK.[2] Vitamin K is a group of structurally similar, fat-soluble vitamins that are needed for the post-translational modification of certain proteins, mostly required for blood coagulation but also involved in metabolic pathways in bone and other tissue.

Vitamin K is capable of blocking the blood thinning action of anticoagulants like warfarin, which work by interfering with the action of vitamin K. They also reverse the tendency of these drugs to cause arterial calcification in the long term. In addition, it has been also validated in previous Cooperstown 5 + 1 cocktail studies.[2] Therefore, in the current study, vitamin K will be dosed with warfarin at the same time to prevent the pharmacodynamics (PDy) effects of warfarin without altering the stereoisomer PK.

1.3.1.2. Midazolam

Midazolam is utilized in this study because it is a known probe substrate of CYP3A4. Midazolam is a short-acting drug in the benzodiazepine class that is used for treatment of acute seizures, moderate to severe insomnia, and for inducing sedation and amnesia before medical procedures. Intravenous midazolam is indicated for procedural sedation (often in combination with an opioid, such as fentanyl), for pre-operative sedation, for the induction of general anesthesia, and for sedation of ventilated patients in critical care units. Oral midazolam is indicated for the short-term treatment of moderately severe insomnia in patients who have not reacted adequately to other hypnotics, and who have persistent trouble in falling asleep.

In adults, midazolam has a t1/2 of 1 to 4 hours; however, in the elderly, as well as young children and adolescents, the t1/2 is longer.

Midazolam is poorly absorbed orally with only 50% of the drug reaching the bloodstream, and midazolam is metabolized by CYP enzymes and by glucuronide conjugation. Midazolam is metabolized into an active metabolite alpha-hydroxymidazolam by CYP3A4. Age-related deficits and renal and liver status affect the PK factors of midazolam as well as its active metabolite.

The therapeutic as well as adverse effects of midazolam are due to its effects on the gamma-aminobutyric acid (GABA) type A receptors; midazolam does not activate GABA type A receptors directly but, as with other benzodiazepines, it enhances the effect of the neurotransmitter GABA on the GABA type A receptors resulting in neural inhibition. Almost all of the properties can be explained by the actions of benzodiazepines on GABA type A receptors.

Potential adverse reactions to midazolam may include:

- Ataxia
- Dysarthria
- Nystagmus
- Slurred speech
- Somnolence (difficulty staying awake)
- Mental confusion
- Hypotension
- Respiratory arrest and
- Vasomotor collapse

Since midazolam is a known and FDA-recommended probe substrate of CYP3A4 (per the FDA, C. C. [2006] Guidance for Industry: drug interaction studies-study design, data analysis, and implications for dosing and labeling) and it has been also validated in previous Cooperstown 5 + 1 cocktail studies,[2] it has been selected in the current study as a probe drug to test the effect of single and multiple doses of pexidartinib on the PK profiles of drugs metabolized by CYP3A4.

1.3.2. Study Purpose

The purpose of this study is to evaluate the effect of pexidartinib on the PK of midazolam and S-warfarin as an assessment of pexidartinib's potential for DDI with substrates of CY3A4 and CYP2C9, respectively. This study will also evaluate the efficacy and safety of pexidartinib treatment in various tumors.

1.4. Risks and Benefits for Study Subjects

Pexidartinib demonstrated pharmacologic and anti-tumor activity in a variety of in vitro and tumor models. It is currently being investigated in a variety of Phase 1-3 studies for the treatment of tumors and TGCT. Evidence of clinical activity has been observed in TGCT.

Safety data for pexidartinib are from nonclinical and clinical studies. Liver toxicity and myelosuppression are important identified risks and embryofetal toxicity is considered as an important potential risk with pexidartinib. Liver toxicity observed in clinical studies includes cases of liver cholestasis with single agent treatment in the Phase 3 PLX108-10 study. Risk minimization measures, such as frequent monitoring during the first 8 wk of pexidartinib treatment, are included in this protocol. Protocol-defined dose reductions and discontinuations of pexidartinib, increased frequency of laboratory monitoring, and reporting of findings should be followed. In addition, rechallenge with pexidartinib should not be attempted without prior discussion with the Sponsor's Medical Monitor.

Risk benefit of pexidartinib should be assessed for each potential patient.

2. STUDY OBJECTIVES AND HYPOTHESIS

2.1. Study Objectives

2.1.1. Primary Objectives

To assess the effects of pexidartinib on the PK parameters of single-dose midazolam and S-warfarin in patients.

2.1.2. Secondary Objectives

To evaluate:

- To determine the overall response rate (ORR) in patients with TGCT, kit-mutant melanoma, kit-mutant GIST, or other tumors
- To assess the safety and tolerability of pexidartinib alone and in combination with single-dose midazolam and S-warfarin
- To determine the safety of pexidartinib given as monotherapy over longer periods
- To evaluate the PK of pexidartinib and ZAAD-1006a

2.1.3. Exploratory Objectives

To evaluate:

- Other measures of efficacy including:
  - Duration of response
  - Time to progression (for TGCT and other non-malignant tumors)
  - Progression-free survival (for malignant tumors)
- Pharmacogenomic (PGx) analysis
- Optional (at the discretion of the Investigator/patient): Pharmacodynamics (PDy) of pexidartinib in treated patients
- Optional (at the discretion of the Investigator/patient): Tumor biomarker analysis

2.2. Study Hypothesis

This study is not hypothesis testing, but is intended to characterize the effects of pexidartinib on the PK parameters of single-dose midazolam and S-warfarin.

2.3. Study Endpoints

2.3.1. Primary Endpoints

PK parameters of midazolam and S-warfarin: Cmax, tmax, and AUClast. If data permits, other PK parameters including t1/2 and AUCinf will be calculated.

2.3.2. Secondary Endpoints

2.3.2.1. PK

- Plasma PK parameters (Cmax, Tmax, AUClast) will be calculated for pexidartinib and its metabolite, ZAAD-1006a
- Plasma PK parameters (Cmax, Tmax, AUClast) will be calculated for midazolam metabolite, 5-hydroxy midazolam and also metabolite to parent ratio (MPR) for 5-hydroxy midazolam and midazolam will be calculated

2.3.2.2. Efficacy

- Best objective response per RECIST 1.1
- Duration of response
- Time to progression (for TGCT and other non-malignant tumors)
- Progression-free survival (for malignant tumors)

2.3.2.3. Safety

- TEAEs
- Vital signs
- Electrocardiograms (ECGs)
- Clinical laboratory tests including AST/ALT/Total bilirubin (TBil)

2.3.3. Exploratory Endpoints

- PGx biomarkers
- Optional: PDy biomarkers
- Optional: Tumor biomarker analysis

3. STUDY DESIGN

3.1. Overall Design

3.1.1. Overview

This open-label, single sequence crossover study will comprise 2 parts:

Part 1: An initial single sequence crossover part to evaluate the effect of pexidartinib on the PK of midazolam and S-warfarin, the DDI Phase.

Part 2: An evaluation of efficacy and safety of pexidartinib treatment in various tumors.

Screening will take place between Day -21 and Day -1. The total duration of participation (excluding Screening) for each patient in Part 1 will be approximately 18 d. Pexidartinib treatment (1000 mg/d) will commence on Day 5. Thereafter, pexidartinib treatment will continue BID into Part 2 of the study at the doses defined below to evaluate efficacy and safety until there is no longer clinical benefit or until other reasons for discontinuation are met.

Part 1:

- On Day 1 patients will receive the single oral dose of midazolam (2 mg) and S-warfarin (10 mg with vitamin K [5 mg]), and PK samples will be collected approximately 48 h and 96 h, respectively.
- On Day 5 (C1D1) pexidartinib (1000 mg/d) in twice daily (BID) dosing will be initiated and continue throughout the remainder of Part 1 and into Part 2. On the first day of pexidartinib treatment (Day 5), a single dose of midazolam (2 mg) and S-warfarin (10 mg with vitamin K [5 mg]) will be co-administered with the morning pexidartinib dose (400 mg), and PK samples will be collected over 10 h (pexidartinib), 48 h (midazolam), or 96 h (S-warfarin).
- On Day 15, a single dose of midazolam (2 mg) and S-warfarin (10 mg with vitamin K [5 mg]) will be co-administered with the morning dose of pexidartinib (400 mg), and PK samples will be collected over 10 h (pexidartinib), 48 h (midazolam), or 96 h (S-warfarin).

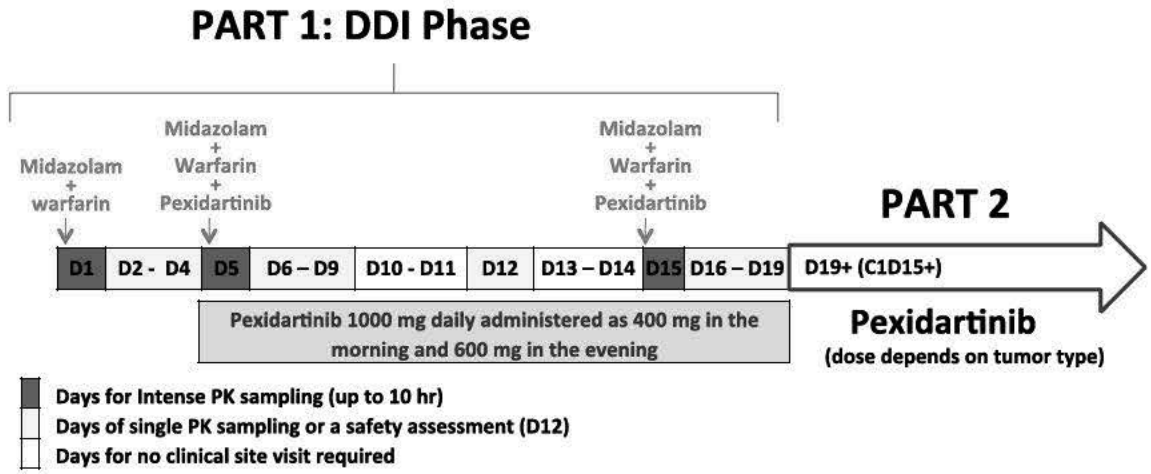
In Part 2, and specifically starting on Day 19 (C1D15) of pexidartinib treatment, the dose of pexidartinib will be reduced to 800 mg/d (400 mg BID) for patients with TGCT or other non-malignant tumors. For patients with malignant tumors, the pexidartinib dose will remain at 1000 mg/d. Patients will be assessed for safety and efficacy. An optional tumor biopsy or archival tumor specimen under specific informed consent and/or blood samples for circulating tumor DNA may be collected at Screening and during pexidartinib treatment for exploratory analysis of tumor biomarkers at the discretion of the Investigator/patient.

Pexidartinib drug will be administered BID, every day, unless criteria for interruption are met (Section 5.4). For the first 2 wk, patients will take 2 capsules in the morning and 3 capsules in the evening, for a total daily dose of 1000 mg/d pexidartinib. Thereafter, for patients with TGCT or other non-malignant tumor, the pexidartinib dose will be reduced

to 2 capsules in the morning and 2 capsules in the evening, for a total daily dose of 800 mg/d pexidartinib. For patients with malignant tumors, the pexidartinib dose will remain at 1000 mg/d unless criteria for dose reduction are met (see below). Each treatment cycle will be 28 d in duration. Dose reductions, interruptions, and re-escalations after previous reductions for toxicity are required according to pre-specified guidelines (see below). Patients will be eligible to continue receiving pexidartinib until disease progression, unacceptable toxicity, the occurrence of other termination criteria, or withdrawal from the study. The primary PK analysis will be performed after the last patient completes the Part 1 assessments. The key efficacy and safety analyses will be completed when all patients have completed 6 cycles of pexidartinib treatment and the Cycle 7 Day 1 (C7D1) assessments or discontinued treatment.

Tumor assessments will be performed locally every 2 cycles through the first 6 cycles of pexidartinib treatment, unless an alternate schedule is appropriate for the tumor and is agreed with the Sponsor. After 4 cycles, the frequency of tumor assessments may be reduced as appropriate for the tumor type. For TGCT, tumor assessments must be based upon magnetic resonance imaging (MRI) scans; for other tumors, MRI, computerized tomography (CT), or other appropriate tumor assessment method maybe used. All tumor assessments will be read locally.

Figure 3.1: Study Schema



3.1.2. Study Stopping Criteria

Not applicable.

3.1.3. Duration of Patient Participation

Patients will be screened no longer than 21 d prior to dosing on Day 1.

The duration of Part 1 of the study will be approximately 18 d for each patient. Part 2 of the study will continue until there is no longer clinical benefit or until other reasons for discontinuation are met.

After all patients have completed the C7D1 assessments or discontinued pexidartinib treatment, the primary efficacy and safety analyses will be performed. Patients remaining on pexidartinib treatment with ongoing clinical benefit may continue in the study thereafter and the extent of assessments and data collection may be reduced upon Investigator and Sponsor discretion.

3.2. Discussion of Study Design

This open-label, single sequence, crossover study design is appropriate to assess the effect of pexidartinib on the PK of midazolam and S-warfarin. The PK of midazolam and S-warfarin will be determined first prior to the administration of pexidartinib to establish reference PK parameters for these compounds in patients. Then, the PK of the midazolam and S-warfarin will be evaluated again upon the initial administration of pexidartinib to evaluate the direct and immediate inhibitory effects of pexidartinib on CYP3A4 and CYP2C9. Finally, the PK of midazolam and S-warfarin will be evaluated again after multiple doses of pexidartinib administration to assess the net effect of possible induction and time-dependent inhibition potential of pexidartinib on CYP3A4 and to assess the effect of pexidartinib direct inhibition of CYP2C9 at steady state exposure of pexidartinib.

After the DDI study in Part 1, pexidartinib administration will continue in this population of patients with untreatable tumors to assess anti-tumor activity and safety of pexidartinib in Part 2.

3.3. Selection of Doses

The study drug doses are as follows:

- S-warfarin: 10 mg with vitamin K (5 mg)
- Midazolam: 2 mg
- Pexidartinib: 1000 mg/d administered as a split dose of 400 mg (am) and 600 mg (pm). The dose will be reduced to 800 mg/d (400 mg BID) for patients with TGCT or other non-malignant tumor after 14 d of treatment. See Section 5.4.

These are commonly used doses for S-warfarin and midazolam. Vitamin K will be administered to prevent the PDy effects of S-warfarin without altering the stereoisomer PK.

4. STUDY POPULATION

Patients must sign and date the Informed Consent Form (ICF) provided by the study site before any study-specific qualification procedures are conducted.

4.1. Inclusion Criteria

Patients must meet the following inclusion criteria to be enrolled in the study:

1. Age ≥ 18 y or ≥ the legal age for being considered as an adult in the country where the patient is screened at the time of signing informed consent.
2. A diagnosis of TGCT, kit-mutant melanoma, kit-mutant GIST, leukemia, or other tumor for which there is no other standard systemic therapy. Patients with TGCT or other non-malignant tumor must be approved by the Sponsor prior to Screening and enrollment. Prior pexidartinib is permitted for TGCT patients unless ineffective or not related and there has been a washout period of at least 4 wk.
3. Women of childbearing potential must have a negative serum pregnancy test within 14 d prior to enrollment. (Where demanded by local regulations, this test may be required within 72 h prior to enrollment).
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, respectively, by using a highly effective contraception method, as described below, throughout the study and up to 90 d after completion. Highly effective methods of contraception include intra-uterine device (nonhormonal or hormonal); bilateral tubal occlusion; vasectomy; sexual abstinence (only if this is in line with the patient's current lifestyle); or barrier methods (eg, condom, diaphragm) used in combination with hormonal methods associated with inhibition of ovulation. Women of nonchildbearing potential may be included if they are either surgically sterile or have been postmenopausal for ≥ 1 y. Women who have documentation of at least 12 mo of spontaneous amenorrhea and have a follicle-stimulating hormone level > 40 mIU/mL will be considered postmenopausal.
5. Adequate hematologic, hepatic, and renal function, defined by:
   - Absolute neutrophil count ≥ 1.5×10^9/L
   - Hemoglobin > 10 g/dL
   - Platelet count ≥ 100×10^9/L
   - AST and ALT ≤ 1.5 × upper limit of normal (ULN)
   - TBil ≤ ULN with an exception of patients with confirmed Gilbert's syndrome. For patients with confirmed Gilbert's syndrome, the TBil should be ≤ 1.5 × ULN
   - Serum creatinine ≤ 1.5 × ULN

6. Willingness and ability to use a pill diary.
7. 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

Patients must not meet the following exclusion criteria to be enrolled in the study:

1. Known active or chronic human immunodeficiency virus (HIV) or hepatitis C virus (HCV) infection, or positive hepatitis B (Hep B) surface antigen.
2. Known active tuberculosis.
3. Hepatobiliary diseases including biliary tract diseases, autoimmune hepatitis, inflammation, fibrosis, cirrhosis of liver caused by viral, alcohol, or genetic reasons. Gilbert's disease is allowed if TBil is $\leq 1.5 \times$ ULN.
4. Women who are breastfeeding.
5. Patients with a poor metabolizer status of CYP2C9.
6. Patients on potent CYP2C9, CYP3A4, and Uridine 5'-diphospho-glucuronosyltransferase family 1 member A4 (UGT1A4) inducer and inhibitors and potent P-glycoprotein (P-gp) inhibitors and inducers, unless these medications are discontinued at least 14 d before study drug administration. Food or beverages containing CYP3A4/5 inhibitors (eg, grapefruit, pomegranate, pomelo, and star fruit) should be avoided throughout the study.
7. A screening Fridericia corrected QT interval (QTcF) $\geq$ 450 ms (men) or $\geq$ 470 ms (women).
8. History of hypersensitivity to any investigational products, including their excipients.
9. Inability to swallow capsules.
10. Inability to complete study procedures.

5. STUDY TREATMENT

5.1. Assigning Patients to Treatment Group/Sequence and Blinding

5.1.1. Treatment Group

This is a single arm study. Patients will receive midazolam (2 mg) and S-warfarin (10 mg) as a single oral dose on Days 1. On Days 5 and 15, patients will receive a single oral dose of midazolam (2 mg), S-warfarin (10 mg), and pexidartinib (400 mg) at the site. Patients will receive also pexidartinib of 1000 mg/d (400 mg in the morning [co-administered with midazolam and S-warfarin on Days 5 and 15] and 600 mg in the evening) starting on Day 5. Thereafter, for Part 2, the dose will be as follows:

- Patients with TGCT or other non-malignant tumors – the dose would be reduced to 800 mg/d (400 mg in the morning and 400 mg in the evening). After patients have been on pexidartinib treatment for at least 6 mo, including possible pexidartinib treatment prior to this study, the dose of pexidartinib may be reduced or otherwise modified, eg, treatment holiday, at Investigator discretion provided that the pexidartinib dose does not exceed 1000 mg/d.
- Patients with malignant tumors – the 1000 mg/d dose will continue into Part 2, unless criteria for dose modification have been met.

5.1.2. Method of Treatment Group/Sequences Allocation

Treatment allocation will not be applied to this single arm design. The study design is described in Section 3.

5.1.3. Blinding

This study is open-label and no blinding will occur.

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 supplied as a 200 mg capsule formulation J 3397 AF (200 mg free base equivalent) for oral administration contains 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.

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

Commercially available S-warfarin and midazolam will be supplied by DS.

5.2.2. Labeling and Packaging

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

5.2.3. Preparation

All pexidartinib will be supplied by the Sponsor, and require no further preparation at the study site.

5.2.4. Administration

Midazolam and S-warfarin will always be administered to enrolled patients after an overnight fast of approximately 10 h to avoid food effects. Administration will be done at the clinical site under the supervision of the principal Investigator or identified sub-Investigator(s). On the intensive PK sampling days, pexidartinib will be administered at the clinical site. The study drug for home administration during the study will be dispensed to the patient for the first time on the evening of pexidartinib treatment initiation. During Part 1, the number of pexidartinib capsules, which is just adequate until next scheduled visit, will be dispensed to ensure no home administration on the PK sampling days. Capsules should be swallowed and not crushed, chewed, or dissolved in liquid. In this study, patients will receive pexidartinib capsules for administration at home; and pexidartinib, midazolam, and S-warfarin will be co-administered in the clinic.

Pexidartinib administration will begin at the Day 5 visit in the morning in Part 1. At this visit, patients will be instructed to take 5 capsules a day for the first 2 wk, 1000 mg/d pexidartinib; this amount will be divided into a morning dose of 2 capsules and an evening dose of 3 capsules. After 2 wk (at the C1D15 visit, after completion of Part 1), the dose will be reduced to 2 capsules in the morning and 2 capsules in the evening (800 mg/d pexidartinib) for patients with TGCT or other non-malignant tumor. Patients who had a dose reduction during the first 2 wk will continue treatment at their reduced dose. Doses should be taken in the fasting state (ie, no food for 1 h before and 2 h after dose administration). During the fasting period, patients will be permitted to eat a low-fat snack (eg, crackers, toast, tea) if needed. Doses will be taken at approximately the same time of the day and approximately 12 h apart. Each dosing cycle will be 28 d.

During Part 1, the patient should be instructed to bring their bottle of study drug to the site and only take their morning dose upon instruction by the study site. The time of dosing should be recorded. Patients will then take their evening dose at home. If dose administered at the site is taken in the afternoon, then the patient should be instructed to skip their evening dose for that day.

Between site visits, patients are to administer their study drug at home and record the dosing information in the study dosing diary. Missed doses (those generally outside of a ± 2 h dosing window) should be skipped and NOT administered as a double dose at the next dosing time point. Patients who vomit their dose should be instructed to NOT make up that dose.

5.2.5. Storage

Drug supplies must be stored in a secure, limited access storage area within the recommended storage conditions. Contact Daiichi Sankyo Inc. if storage conditions go outside the specified range. All drug supplies should be quarantined pending decision from Daiichi Sankyo Inc.

5.2.6. Drug Accountability

When a drug shipment is received, the Investigator or designee is to check the amount, condition and temperature recording of the drug, the appropriate local language is used on the label, and the drug expiration date, and to sign the Receipt of Shipment Form provided.

In addition, the Investigator or designee shall contact Daiichi Sankyo Inc. or designee as soon as possible if there is a problem with the shipment.

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

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

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

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

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

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

5.2.7. Retention Samples

Not applicable.

5.3. Control Treatment

Not applicable.

5.4. 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 in Table 5.1. Dose reduction/interruption guidelines for hematologic and nonhematologic treatment-related TEAEs are based on severity. Dose interruptions can be implemented at the discretion of the treating 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.

When an odd number of capsules are 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 and 2 capsules in the evening). When an even number of capsules per day is to be taken, the morning and evening doses should be the same (eg, 800 mg/d = 4 capsules [2 capsules in the morning and 2 capsules in the evening] or 400 mg/d = 2 capsules [1 capsule in the morning and 1 capsule in the evening]).

Dose reductions should be applied in increments of 200 mg/d (1 capsule). Patients unable to tolerate 400 mg/d (2 capsules) will be discontinued. Once dose reduction takes place for toxicity, a dose re-escalation is generally not allowed unless approved after discussion with the Daiichi Sankyo Inc. Medical Monitor or designee.

Dose modification guidelines for treatment-related toxicities as well as guidelines for their management are presented in Table 5.1, Table 5.2, and Table 5.3. These parameters are only a guide and are not intended to supersede the clinical judgment of the treating Investigator. All adjustments should be communicated to Daiichi Sankyo Inc.'s Medical Monitor or designee.

Once a patient reduces the dose of study drug, no further probe drugs will be administered to that patient, and he/she will be excluded from the PK Evaluable Set.

Table 5.1: Dose Modification Guidelines for Treatment-Related Toxicities, Excluding Liver Function

Toxicity Grade (CTCAE v4.0), Frequency	When to Hold or Stop	When and How to Restart Dosing
■ Hematologic – Grade 3 or 4 neutropenia		
1st appearance	Interrupt until ANC recovers to ≥ 1×10^9/L; growth factor support	If recovered to ANC ≥ 1×10^9/L in ≤ 7 d, resume at same dose. If not recovered to ANC ≥ 1×10^9/L in ≤ 7 d, reduce dose by 1 capsule.
2nd appearance	Interrupt until ANC recovers to ≥ 1×10^9/L; growth factor support	If recovered to ANC ≥ 1×10^9/L in ≤ 7 d, reduce dose by 1 capsule. If not recovered to ANC ≥ 1×10^9/L in ≤ 7 d, reduce dose by an additional capsule.
3rd appearance	Interrupt until ANC recovers to ≥ 1×10^9/L	If recovered to ANC ≥ 1×10^9/L in ≤ 7 d, reduce dose by 1 capsule. If not recovered to ANC ≥ 1×10^9/L in ≤7 d, discontinue permanently.
4th appearance	Discontinue permanently	n/a
■ Hematologic Grade 3 or 4 febrile neutropenia		
1st appearance	Interrupt until ANC and fever recover; provide growth factor support	Once resolved to ANC ≥ 1×10^9/L and T ≤ 38°C, reduce dose by 1 capsule.
2nd appearance	Interrupt until ANC and fever recover; provide growth factor support	Once resolved to ANC ≥ 1×10^9/L and T ≤ 38°C, reduce dose by an additional capsule.
3rd appearance	Discontinue permanently	n/a

AE = adverse event; ALT = alanine aminotransferase; ANC = absolute neutrophil count; AST = aspartate aminotransferase; CTCAE = Common Terminology Criteria for Adverse Events; n/a = not applicable; PLT = platelets; T = temperature.

[a] Dose interruptions for Grade 2 AEs may be instituted at the discretion of the treating physician after discussion with the Daiichi Sankyo Inc. Medical Monitor or designee.

Table 5.1: Dose Modification Guidelines for Treatment-Related Toxicities, Excluding Liver Function (Continued)

■ Hematologic – Grade 3 or 4 thrombocytopenia		
1st appearance	Interrupt until PLT $\geq 75 \times 10^9$/L	Reintroduce at the same dose.
2nd appearance	Interrupt until PLT $\geq 75 \times 10^9$/L	If PLT does not recover to $\geq 75 \times 10^9$/L in $\leq$ 7 d, reduce dose by 1 capsule.
3rd appearance	Interrupt until PLT $\geq 75 \times 10^9$/L	Reduce dose by an additional capsule.
4th appearance	Discontinue permanently	n/a
■ Nonhematologic Grade 3[a] (excluding transaminase increases [AST/ALT]): start symptomatic treatment when possible		
1st appearance	Interrupt until resolved (Grade 0-1)	If recovered in < 5 d, resume at same dose. Reduce by 1 capsule if symptoms persist for ≥ 5 d despite supportive management.
2nd appearance	Interrupt until resolved (Grade 0-1)	Reduce by an additional capsule.
3rd appearance	Discontinue permanently	n/a
■ Nonhematologic Grade 4 (excluding transaminase increases [AST/ALT]): start symptomatic treatment when possible		
1st appearance	Interrupt until resolved (Grade 0-1)	Reduce by 1 capsule.
2nd appearance	Discontinue permanently	n/a

AE = adverse event; ALT = alanine aminotransferase; ANC = absolute neutrophil count; AST = aspartate aminotransferase; CTCAE = Common Terminology Criteria for Adverse Events; n/a = not applicable; PLT = platelets; T = temperature.

[a] Dose interruptions for Grade 2 AEs may be instituted at the discretion of the treating physician after discussion with the Daiichi Sankyo Inc. Medical Monitor or designee.

Table 5.2: Dose Modification Guidelines for Liver Function Abnormalities

Toxicity Grade CTCAE v0.4	Initial Action	Outcome	Action
ALT or AST Grade 2 (> 3-5 × ULN); No increase in bilirubin[a]	Re-check ALT and AST immediately Hold study drug Monitor weekly[b] Check for changes to medications and for symptoms	Resolution to Grade 0-1 or baseline (no bilirubin increase)	Restart on resolution Grade 0-1 or baseline at 1 dose lower (reduce by one 200 mg capsule)
Grade 3 ALT or AST increase (> 5-20 × ULN); No increase in bilirubin[a]	Re-check ALT and AST immediately Hold study drug Monitor 2x/wk[b] Check for changes to medications and for symptoms	Resolution to Grade 0-1 or baseline (no bilirubin increase) within 14 d	Restart on resolution to Grade 0-1 or baseline at 1 dose lower (reduce by one 200 mg capsule)
		ALT and AST not decreasing within 14 d of holding study drug	Proceed to liver evaluation as outlined below. Restart only on resolution to Grade 0-1/baseline at 1 dose lower (reduce by one 200 mg capsule); For max AST or ALT > 8 × ULN, consult with medical monitor prior to re-start
Grade 4 ALT or AST (> 20 × ULN)	Discontinue treatment Monitor 2x/wk until resolution to Grade 2 Follow-up until resolution Grade 0-1 or baseline Check for changes to medications and for symptoms	All outcomes	Discontinue treatment; Proceed to liver evaluation as outlined below; If clear confirmed alternate cause, restart on resolution to Grade 0-1 or baseline at 1 dose lower (reduce by one 200 mg capsule)
Any grade ALT or AST increase[a] with any bilirubin increase or signs of hypersensitivity	Discontinue treatment Monitor 2x/wk until resolution to Grade 2 Follow-up until resolution Grade 0-1 or baseline Check for changes to medications and for symptoms	All outcomes	Discontinue treatment; Proceed to liver evaluation as outlined below; If clear confirmed alternate cause, restart on resolution to Grade 0-1 or baseline at 1 dose lower (reduce by one 200 mg capsule)

ALT = alanine aminotransferase; AST = aspartate aminotransferase; CTCAE = Common Terminology Criteria for Adverse Events; ULN = upper limit of normal.

a. An increase in bilirubin is defined as all of the following: total bilirubin > ULN, total bilirubin > 20% above baseline, and direct bilirubin is > ULN. If all of these conditions are met, then bilirubin is considered increased and should be immediately re-checked. Pexidartinib treatment should be immediately discontinued for increased bilirubin unless and until there is a clear, confirmed alternate cause.

b. If ALT, AST, or bilirubin worsens during the monitoring period, follow the applicable guidance for the worst toxicity grade.

Table 5.3: Additional Liver Evaluation

Evaluation	Comments
Increase frequency of testing liver chemistries to twice per wk, 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.	

Ig = Immunoglobulin; INR = international normalized ratio; OTC = over-the-counter.

For suspected cases of cholestatic liver injury, eg, aminotransferase increase concurrent with hyperbilirubinemia, or liver biopsy suggesting cholestasis 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.

5.5. Method of Assessing Treatment Compliance

Pexidartinib will be dispensed to patients at the study visits indicated in the Schedule of Events. The appropriate study personnel will document and maintain records of study drug dispensed to each patient and any returns at each study visit.

Patients will complete a dosing diary to record the number of capsules/date/time the dose was taken during each dosing cycle.

At each site visit, patients will be assessed for compliance with study drug administration, ie, actual capsules taken/expected capsules taken. If there is a dose reduction, the number of expected capsules taken should be adjusted accordingly. The patient must also return all bottles (used/unused) at each dispensing visit. Returned capsules must be recorded in the Drug Accountability log.

Further details can be found in the Study Reference Manual.

5.6. Prior and Concomitant Medications

No potent inhibitors or inducers of CYP3A4, CYP2C9, UGT1A4, and P-gp are allowed from 14 d before C1D1 through the completion of Part 1. No systemic pH modifiers are permitted during Part 1. Also, no additional administration of midazolam and S-warfarin beyond the protocol-defined administrations is permitted during this time. Pexidartinib exposure is reduced when administered with pH modifiers like esomeprazole. Therefore, pH modifiers should be avoided 14 d before dosing. Nonsystemic pH modifiers such as antacids can be taken 4 h after pexidartinib administration.

Otherwise, 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 source document and electronic Case Report Form (eCRF), including the reason for treatment, name of the drug, dosage, route, and date of administration. All medications including prescription, over-the-counter (OTC), herbal and other nutritional vitamins and/or supplements taken within 28 d of C1D1 will be recorded on the eCRF. Analgesic use and analgesic regimen will be recorded.

Anti-cancer therapy, including antibody, retinoid, or hormonal treatment (except megestrol acetate as supportive care), and radiation will not be permitted within 2 wk before dosing.

Patients enrolled in studies with pexidartinib and receiving concomitant warfarin, except for the protocol-required administrations, should have their anticoagulation status carefully monitored, especially shortly after initiation of pexidartinib, for the potential need to make adjustments in warfarin dosing. In particular, international normalized ratio (INR) should be obtained just prior to initiation of pexidartinib, within 1 to 2 wk after initiation, and periodically thereafter. Dose adjustments of warfarin should be made as medically indicated.

Of the 5 major CYP isoforms, 3A4 may be involved in Phase 1 metabolism of pexidartinib, with possibly CYP1A2 playing a minor role. Until information regarding exposure-toxicity and exposure-response relationships is available with pexidartinib, concomitant CYP3A4 inhibitors and inducers should be administered with caution, in the event they alter the systemic exposure to pexidartinib (see Section 17.1 for a list of common CYP3A4 inhibitors and inducers). In general, strong inhibitors or inducers of CYP3A4 should be avoided unless clinically necessary. These include anticonvulsants, certain mycin antimicrobials, and antiretrovirals. Some common examples include inhibitors such as erythromycin, clarithromycin, and inducers such as rifampicin, carbamazepine, phenytoin, efavirenz, and nevirapine.[4]

The following medications and products will be prohibited:

- Other investigational agents/devices.
- Pexidartinib is a substrate for CYP3A4/5 and some fruits are CYP3A4/5 inhibitors. Foods or beverages containing CYP3A4/5 inhibitors (eg, grapefruit, pomegranate, pomelo, and star fruit) should be therefore avoided throughout the study.

5.6.1. Dietary and Lifestyle Restrictions

Study drugs will be administered at the clinical site orally with 240 mL of water following at least a 10 h overnight fast. For pexidartinib home dosing, patients will fast 1 h before pexidartinib dosing and continue to fast for 2 h after dosing.

Potent CYP2C9, CYP3A4, and UGTA4 inducer and inhibitors (see Section 17.1) and potent P-gp inhibitors and inducers must be discontinued at least 14 d before study drug administration. No systemic pH modifiers are permitted during Part 1. Nonsystemic pH modifiers such as antacids can be taken 4 h after pexidartinib administration.

Except when ECGs are performed, patients will remain seated in an upright position with minimal ambulation (ie, only to and from the washroom or for study procedures) for the first 4 h following dosing.

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, respectively, by using a highly effective contraception method, as described below, throughout the study and up to 90 d after completion. Highly effective methods of contraception include intra-uterine device (nonhormonal or hormonal); bilateral tubal occlusion; vasectomy; sexual abstinence (only if this is in line with the patient's current lifestyle); or barrier methods (eg, condom, diaphragm) used in combination with hormonal methods associated with inhibition of ovulation. Women of nonchildbearing potential may be included if they are either surgically sterile or have been postmenopausal for ≥1 y. Women who have documentation of at least 12 mo of spontaneous amenorrhea and have a follicle stimulating hormone level > 40 mIU/mL will be considered postmenopausal.

5.7. Patient Withdrawal/Discontinuation

5.7.1. Reasons for Withdrawal

The reason for discontinuation should be recorded for any patient discontinuing from the study.

The reasons a patient may discontinue or be withdrawn from the study permanently include but are not limited to:

- AE
- Disease progression
- Patient request
- Investigator decision

- Protocol violation
- Surgery
- Patient noncompliance
- Pregnancy
- Study termination by Daiichi Sankyo Inc. or institutional review board (IRB)/independent ethics committee (IEC)

5.7.2. Withdrawal Procedures

If a patient 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 dose and the reason for withdrawal.

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

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

When a patient discontinues or is permanently withdrawn from the study, the Investigator will notify Daiichi Sankyo Inc. and ensure that the procedures listed in the "posttreatment visit" column in the Schedule of Events are performed 28 d ± 7 d after the patient's last dose of study drug.

The consequence of a patient's withdrawal of all consent will be that no new information will be collected from that patient and added to the existing data or any database. However, every effort should be made to follow all patients for safety.

The reason for study withdrawal will be recorded.

5.7.3. Patient Replacement

Patients withdrawn from the study will not be replaced except if needed to achieve the target number of evaluable patients for the DDI PK analysis.

5.7.4. Patient Re-Screening Procedures

Re-screening is permitted for any candidate who failed to meet the eligibility criteria upon initial screening. The subject identification number must remain the same at the time of re-screening. The initial screening information and the reason why the patient was ineligible for the initial evaluation will be recorded on the Screening log. No data from the initial evaluation will be entered into the clinical database for a patient who is re-screened.

6. STUDY PROCEDURES

Patients should arrive to the clinical site fasted (approximately 10 h) on Study Days 1, 5, and 15.

6.1. Informed Consent

Signed informed consent must be collected before any study-related procedures are performed.

6.2. Screening

6.2.1. Screening (Day -21 to Day -1)

The following procedures must be performed within the 21 d period before enrollment unless otherwise noted, and the results must be obtained and evaluated for eligibility prior to the enrollment:

- Collect signed informed consent
- Collect prior and concomitant medications
- Collect demographic information
- Collect medical/surgical history
- Measure height and weight
- Perform physical examination
- Record vital signs, measured after patient has rested in the recumbent position for 5 min or more
- Perform 12-lead ECG, collected after patient has rested in the supine position for 5 min or more
- Perform pregnancy testing on women of childbearing potential only
- Collect blood sample for:
  - Serum chemistry, hematology, and coagulation
  - Follicle-stimulating hormone (FSH) level, for postmenopausal women only
- Collect urine sample for urinalysis
- Perform drug and alcohol screening
- Perform tumor assessment
- Collect PGx sample and submit for analysis of metabolizer status of CYP2C9 to determine eligibility
- Perform optional tumor biopsy under specific informed consent and/or blood sample for circulating tumor DNA at the discretion of the Investigator/patient

6.3. Part 1 – Treatment Period

6.3.1. Part 1 – Day 1

The following assessments will be performed on Day 1 of Part 1:

- Perform physical examination
- Measure weight
- Collect blood sample for:
  - Predose serum chemistry and hematology
  - PK sampling for midazolam (predose, 0.5, 1, 2, 3, 4, 6, 8, and 10 [±10 min up to 1 h, ±10% thereafter] h postdose)
  - PK sampling for S-warfarin (predose, 0.5, 1, 2, 3, 4, 6, 8, and 10 [±1] h postdose)
  - Predose PGx sampling
- Record vital signs (predose and 2 and 4 h postdose), measured after patient has rested in the recumbent position for 5 min or more
- Perform 12-lead ECG (predose), measured after the patient has rested in the supine position for 5 min or more
- Co-administer midazolam and S-warfarin (with Vitamin K) at the clinical site
- Record concomitant medications
- Assess AEs

6.3.2. Part 1 – Day 2

The following assessments will be performed on Day 2 of Part 1:

- Record concomitant medications
- Assess AEs
- Collect blood sample for:
  - PK sampling for midazolam (24 [±10%] h postdose)
  - PK sampling for S-warfarin (24 [±2] h postdose)

6.3.3. Part 1 – Day 3

The following assessments will be performed on Day 3 of Part 1:

- Record concomitant medications
- Assess AEs

- Collect blood sample for:
  - PK sampling for midazolam (48 [±10%] h postdose)
  - PK sampling for S-warfarin (48 [±2] h postdose)

6.3.4. Part 1 – Day 4

The following assessments will be performed on Day 4 of Part 1:

- Record concomitant medications
- Assess AEs
- Collect blood sample for PK sampling for S-warfarin (72 [±2] h postdose)

6.3.5. Part 1 – Day 5 (C1D1)

The following assessments will be performed on Day 5 of Part 1 (C1D1):

Note: Patients may delay the Day 5 visit up to 2 days, in which case the 96 h sample from Day 1 should be collected on Day 5 or up to 1 d later. Day 5 is the start of the first 28-d pexidartinib cycle.

- Perform physical examination
- Record concomitant medications
- Assess AEs
- Measure weight
- Collect blood sample for:
  - Predose serum chemistry and hematology
  - PK sampling for midazolam (predose, 0.5, 1, 2, 3, 4, 6, 8, and 10 [±10 min up to 1 h, ±10% thereafter] h)
  - PK sampling for S-warfarin (predose, 0.5, 1, 2, 3, 4, 6, 8, and 10 [±1] h)
  - PK sampling for pexidartinib and ZAAD-1006a (predose, 0.5, 1, 2, 3, 4, 6, 8, and 10 [±1] h)
- Record vital signs (predose and 2 and 4 h postdose), measured after patient has rested in the recumbent position for 5 min or more
- Perform 12-lead ECG (predose), measured after the patient has rested in the supine position for 5 min or more
- Co-administer midazolam, S-warfarin (with Vitamin K), and pexidartinib at the clinical site
- Dispense pexidartinib capsules for evening dose or administer at the clinic

6.3.6. Part 1 – Day 6 (C1D2)

The following assessments will be performed on Day 6 of Part 1:

- Record concomitant medications
- Assess AEs
- Collect blood sample for:
  - PK sampling for midazolam (24 [±10%] h postdose)
  - PK sampling for S-warfarin (24 [±2] h postdose)
- Administer pexidartinib morning dose, preferably at the clinic
- Assess pexidartinib treatment compliance (if applicable)
- Dispense pexidartinib capsules

6.3.7. Part 1 – Day 7 (C1D3)

The following assessments will be performed on Day 7 of Part 1 (C1D3):

- Record concomitant medications
- Assess AEs
- Collect blood sample for:
  - PK sampling for midazolam (48 [±10%] h postdose)
  - PK sampling for S-warfarin (48 [±2] h postdose)
- Administer pexidartinib morning dose, preferably at the clinic
- Assess pexidartinib treatment compliance
- Dispense pexidartinib capsules

6.3.8. Part 1 – Day 8 (C1D4)

The following assessments will be performed on Day 8 of Part 1 (C1D4):

- Record concomitant medications
- Assess AEs
- Collect blood sample for PK sampling for S-warfarin (72 [±2] h postdose)
- Administer pexidartinib morning dose, preferably at the clinic
- Assess pexidartinib treatment compliance
- Dispense pexidartinib capsules

6.3.9. Part 1 – Day 9 (C1D5)

The following assessments will be performed on Day 9 of Part 1 (C1D5).

Note: Patients may delay the Day 9 visit up to 1 d:

- Record concomitant medications
- Assess AEs
- Predose serum chemistry and hematology (Alkaline phosphatase, ALT, AST, total and direct bilirubin, and gamma-glutamyl transferase [GGT] must be evaluated for the possible need to modify pexidartinib treatment before the patient leaves the clinic)
- Collect blood sample for S-warfarin (96 [±2] h postdose); can be delayed by 1 d
- Administer pexidartinib morning dose, preferably at the clinic
- Assess pexidartinib treatment compliance
- Dispense pexidartinib capsules

6.3.10. Part 1 – Day 15 (C1D11)

The following assessments will be performed on Day 15 of Part 1 (C1D11):

Note: May be delayed up to 1 d for patients with TGCT or other non-malignant tumor or up to 4 d for patients with malignant disease, if needed. This visit cannot be delayed by more than 1 d for patients with TGCT or other non-malignant tumor because they require a pexidartinib dose reduction to 800 mg/d after 14 d of treatment that cannot be completed before the last PK sample is taken. If the Part 1 Day 15 visit is delayed, pexidartinib BID administration and weekly safety assessments must continue (±1 d) despite the delay. The cycle day count begins from the first dose of pexidartinib (C1D1) and continues regardless of any delay.

- Perform physical examination
- Record concomitant medications
- Assess AEs
- Measure weight
- Collect blood samples for:
  - Predose chemistry and hematology (Alkaline phosphatase, ALT, AST, total and direct bilirubin, and GGT must be evaluated for the possible need to modify pexidartinib treatment before the patient leaves the clinic)
  - PK sampling for midazolam (predose, 0.5, 1, 2, 3, 4, 6, 8, and 10 [±10 min up to 1 h, ±10% thereafter] h postdose)

  - PK sampling for S-warfarin (predose, 0.5, 1, 2, 3, 4, 6, 8, and 10 [±1] h postdose)
  - PK sampling for pexidartinib and ZAAD-1006a (predose, 0.5, 1, 2, 3, 4, 6, 8, and 10 [±1] h postdose)
- Record vital signs (predose and 2 and 4 h postdose), measured after patient has rested in the recumbent position for 5 min or more
- Perform 12-lead ECG (predose), measured after the patient has rested in the supine position for 5 min or more
- Co-administer midazolam, S-warfarin (with Vitamin K), and pexidartinib at the clinical site
- Assess pexidartinib treatment compliance
- Dispense pexidartinib capsules for evening dose or administer at the clinic

6.3.11. Part 1 – Day 16 (C1D12)

The following assessments will be performed on Day 16 of Part 1 (C1D12):

- Record concomitant medications
- Assess AEs
- Collect blood samples for:
  - PK sampling for midazolam (24 [±10%] h postdose)
  - PK sampling for S-warfarin (24 [±2] h postdose)
- Administer pexidartinib morning dose, preferably at the clinic
- Assess pexidartinib treatment compliance
- Dispense pexidartinib capsules

6.3.12. Part 1 – Day 17 (C1D13)

The following assessments will be performed on Day 17 of Part 1 (C1D13):

- Record concomitant medications
- Assess AEs
- Collect blood samples for:
  - PK sampling for midazolam (48 [±10%] h postdose)
  - PK sampling for S-warfarin (48 [±2] h postdose)
- Administer pexidartinib morning dose, preferably at the clinic
- Assess pexidartinib compliance
- Dispense pexidartinib capsules

6.3.13. Part 1 – Day 18 (C1D14)

The following assessments will be performed on Day 18 of Part 1 (C1D14).

- Record concomitant medications
- Assess AEs
- Perform physical examination (or upon early withdrawal); may be done after last PK draw on the final day of the Part 1 DDI Phase
- Collect blood sample for S-warfarin (72 [±2] h postdose)
- Administer pexidartinib morning dose, preferably at the clinic
- Assess pexidartinib treatment compliance
- Dispense pexidartinib capsules

6.4. Part 2 – Treatment Period

6.4.1. Part 2 – Day 19 (C1D15)

The following assessments will completed on Day 19 of Part 2 (C1D15):

Note: Patients may delay the Day 19 visit by 1 d.

- Record concomitant medications.
- Assess AEs.
- Record vital signs (predose), measured after patient has rested in the recumbent position for 5 min or more.
- Perform 12-lead ECG (predose), measured after the patient has rested in the supine position for 5 min or more.
- Collect blood samples for:
  - Predose serum chemistry and hematology. (Alkaline phosphatase, ALT, AST, total and direct bilirubin, and GGT must be evaluated for the possible need to modify pexidartinib treatment before the patient leaves the clinic).
  - PK sample for S-warfarin (96 [±2] h postdose); can be delayed by 1 d.
- Collect urine sample for urinalysis.
- Assess pexidartinib treatment compliance.
- Dispense pexidartinib capsules; for patients with TGCT or other benign tumors, the pexidartinib dose should be reduced to 800 mg/d (400 mg BID) after 14 d of treatment.

6.4.2. Part 2 – Day 26 (C1D22)

The following assessments will be performed on Day 28 (±2 d) of Part 2 (C1D22):

- Record concomitant medications.
- Assess AEs.
- Collect blood sample for predose serum chemistry and hematology. (Alkaline phosphatase, ALT, AST, total and direct bilirubin, and GGT must be evaluated for the possible need to modify pexidartinib treatment before the patient leaves the clinic).
- Dispense pexidartinib capsules.
- Assess pexidartinib treatment compliance.

6.4.3. Part 2 – Day 33 (C2D1)

The following assessments will be performed on Day 33 (±2 d) of Part 2:

- Record concomitant medications.
- Assess AEs.
- Perform physical examination.
- Collect blood sample for predose serum chemistry and hematology. (Alkaline phosphatase, ALT, AST, total and direct bilirubin, and GGT must be evaluated for the possible need to modify pexidartinib treatment before the patient leaves the clinic).
- Record vital signs (predose), measured after patient has rested in the recumbent position for 5 min or more.
- Perform pregnancy test for women of childbearing potential only.
- Dispense pexidartinib capsules.
- Assess pexidartinib treatment compliance.
- Perform optional tumor biopsy under specific informed consent or blood sample for circulating tumor DNA at the discretion of the Investigator/patient.

6.4.4. Part 2 – Day 40 (C2D8)

The following assessments will be performed on Day 40 (±2 d) of Part 2 (C2D8):

- Record concomitant medications.
- Assess AEs.
- Collect blood sample for predose serum chemistry and hematology. (Alkaline phosphatase, ALT, AST, total and direct bilirubin, and GGT must be evaluated for the possible need to modify pexidartinib treatment before the patient leaves the clinic).

- Dispense pexidartinib capsules.
- Assess pexidartinib treatment compliance.

6.4.5. Part 2 – Day 47 (C2D15)

The following assessments will be performed on Day 47 (±2 d) of Part 2 (C2D15):

- Record concomitant medications.
- Assess AEs.
- Collect blood sample for predose serum chemistry and hematology. (Alkaline phosphatase, ALT, AST, total and direct bilirubin, and GGT must be evaluated for the possible need to modify pexidartinib treatment before the patient leaves the clinic).
- Dispense pexidartinib capsules.
- Assess pexidartinib treatment compliance.

6.4.6. Part 2 – Day 54 (C2D22)

The following assessments will be performed on Day 54 (±2 d) of Part 2 (C2D22):

- Record concomitant medications.
- Assess AEs.
- Collect blood sample for predose serum chemistry and hematology. (Alkaline phosphatase, ALT, AST, total and direct bilirubin, and GGT must be evaluated for the possible need to modify pexidartinib treatment before the patient leaves the clinic).
- Dispense pexidartinib capsules.
- Assess pexidartinib treatment compliance.

6.4.7. Part 2 – Day 61 (C3D1)

The following assessments will be performed on Day 61 (±2 d) of Part 2 (C3D1):

- Record concomitant medications.
- Assess AEs.
- Perform tumor assessment.
- Collect blood sample for predose serum chemistry and hematology. (Alkaline phosphatase, ALT, AST, total and direct bilirubin, and GGT must be evaluated for the possible need to modify pexidartinib treatment before the patient leaves the clinic).
- Record vital signs (predose), measured after patient has rested in the recumbent position for 5 min or more.
- Perform pregnancy test for women of childbearing potential only.

- Dispense pexidartinib capsules.
- Assess pexidartinib treatment compliance.

6.4.8. Part 2 – Day 75 (C3D15)

The following assessments will be performed on Day 75 (±7 d) of Part 2 (C3D15):

- Record concomitant medications.
- Assess AEs.
- Collect blood sample for predose serum chemistry and hematology. (Alkaline phosphatase, ALT, AST, total and direct bilirubin, and GGT must be evaluated for the possible need to modify pexidartinib treatment before the patient leaves the clinic).
- Assess pexidartinib treatment compliance.
- Dispense pexidartinib capsules.

6.4.9. Part 2 – Day 89 (C4D1)

The following assessments will be performed on Day 89 (±7 d) of Part 2 (C4D1):

- Record concomitant medications.
- Assess AEs.
- Perform physical examination.
- Collect blood sample for predose serum chemistry and hematology. (Alkaline phosphatase, ALT, AST, total and direct bilirubin, and GGT must be evaluated for the possible need to modify pexidartinib treatment before the patient leaves the clinic).
- Record vital signs (predose), measured after patient has rested in the recumbent position for 5 min or more.
- Perform pregnancy test for women of childbearing potential only.
- Assess pexidartinib treatment compliance.
- Dispense pexidartinib capsules.
- Perform optional tumor biopsy under specific informed consent or blood sample for circulating tumor DNA at the discretion of the Investigator/patient.

6.4.10. Part 2 – Day # (C5+D1)

Note: The 28-d treatment cycles will continue until there is no longer any clinical benefit or until other reasons for discontinuation are met.

The following assessments will be performed during the remainder of the study cycles on Day 1 (±7 d) of that cycle unless otherwise specified:

- Record concomitant medications.
- Assess AEs.
- Perform physical examination every 2 cycles.
- Perform tumor assessment every 2 cycles. May be reduced after Cycle 4 if clinically appropriate and approved by the Sponsor's Medical Monitor.
- Collect blood sample for predose serum chemistry and hematology. (Alkaline phosphatase, ALT, AST, total and direct bilirubin, and GGT must be evaluated for the possible need to modify pexidartinib treatment before the patient leaves the clinic).
- Record vital signs (predose), measured after patient has rested in the recumbent position for 5 min or more.
- Perform pregnancy test for women of childbearing potential only.
- Assess pexidartinib treatment compliance.
- Dispense pexidartinib capsules.

6.5. Posttreatment

The following assessments will be performed 28 d (±7 d) after the last dose:

- Record concomitant medications.
- Assess AEs.
- Perform physical examination.
- Perform 12-lead ECG, measured after the patient has rested in the supine position for 5 min or more.
- Collect urine for urinalysis.
- Collect blood sample for serum chemistry and hematology.
- Record vital signs, measured after patient has rested in the recumbent position for 5 min or more.
- Perform pregnancy test for women of childbearing potential only.

7. PHARMACOKINETIC/PHARMACODYNAMIC ASSESSMENTS

Patients will be assessed for the PK and optional PDy endpoints at the discretion of the Investigator/patient.

7.1. Pharmacokinetic Assessment(s)

PK parameters of midazolam and S-warfarin: Cmax, Tmax, and AUClast. Other PK parameters including t1/2 and AUCinf will also be calculated. For 5-hydroxy midazolam, Cmax, Tmax, AUClast, and AUCinf will be calculated. Additionally, MPR for 5-hydroxy midazolam and midazolam will also be calculated.

PK parameters (Cmax, tmax, and AUClast) will be calculated for pexidartinib and its primary metabolite, ZAAD-1006a after the first dose and multiple doses.

PK sampling will be performed at the study visits indicated in the Schedule of Events:

- Plasma samples for midazolam will be collected at predose, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 24, and 48 h (±10 min up to 1 h, ±10% thereafter) on Day 1 to 3 and also when co-administered with pexidartinib on Days 5 to 7 and Days 15 to 17. These samples will also be analyzed for 5-hydroxy midazolam.
- Plasma samples for S-warfarin will be collected predose, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10 (±1), 24 (±2), 48 (±2), 72 (±2), and 96 (±2) h on Days 1 to 5 and also when co-administered with pexidartinib on Days 5 to 9 and Days 15 to 19.
- Plasma samples for pexidartinib and its metabolites will be collected at predose, 0.5, 1, 2, 3, 4, 6, 8, and 10 (±1) h after the first dose on Day 5 and at steady state when co-administered with midazolam and S-warfarin on Day 15.

Patients should be told to NOT take the morning dose of study drug on the days of PK sampling. Additionally, only an adequate number of capsules to cover dosing till the next clinic visit will be dispensed.

The exact time of dose administration should be recorded along with the corresponding PK blood samplings. The exact time of the 3 preceding doses should also be recorded.

Blood samples of approximately 3 mL for PK analyses will be collected at the time points specified in the Schedule of Events.

Detailed instructions on collection, processing, handling, storage, and sample shipment are provided in the Laboratory Manual.

7.2. Pharmacodynamic Assessment

Plasma for circulating PDy biomarkers may be collected optionally at the discretion of the Investigator/patient as defined in the Schedule of Events and analyzed for PDy biomarkers of pexidartinib.

Detailed instructions on collection, processing, handling, storage, and sample shipment is provided in the Laboratory Manual.

7.3. Immunogenicity

Not applicable.

7.4. Pharmacogenomic Analysis

7.4.1. Genomic or Genetic Banking and Analysis

A blood sample (10 mL) for PGx analysis will be collected from each patient at Screening and at predose on Day 1 (Period 1) of the study.

The following procedures will be used for the long-term preservation (banking) of deoxyribonucleic acid specimens extracted from patients' blood samples. Pharmacogenomic samples may be analyzed for genes involved in absorption, distribution, metabolism, elimination, safety, and efficacy 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. Deoxyribonucleic acid 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 are provided below and will be included in the procedures manual.

7.4.2. Metabolizers for CYP2C19

A genotyping blood sample will be taken at Screening to identify and exclude CYP2C9 poor metabolizers. Patients with poor metabolizer genotype status for CYP2C9 will be excluded from the study to ensure that the study population is sensitive to a potential interaction and to reduce variability.

Poor metabolizers are defined as follows:

- CYP2C9 poor metabolizer status will be determined by genotyping CYP2C9 *2 (rs1799853) and CYP2C9 *3 (rs1057910). Patients with the CYP2C9 *2/*2, *2/*3 or *3/*3 genotypes will be considered CYP2C9 poor metabolizers.

7.4.2.1. Collection of Specimens for Genomic or Genetic Banking and Analysis

On the morning of Screening and Day 1 (Period 1) pre-dose, a 10-mL blood sample for PGx analysis will be collected from patients. The sample will be collected into a 10 mL K_2EDTA polypropylene blood collection tube. It is very important to collect a full tube.

Each sample must be labeled with a unique identifier. GLP requires a chain of custody that is traceable to the sample donor. In order to ensure patient confidentiality, sample tubes will be identified only by patient identification number.

Labels must be legible and waterproof. It is recommended that labels be created using waterproof ink and covered with clear label tape.

The tubes should be placed in an ice bath immediately following collection and then stored upright in a freezer set at -20°C (± 10°C) until packed for shipping.

The following shipping procedures are to be followed:

1. Prepare samples for shipment only on the day of transit. The samples must be shipped on the first available day following collection.
2. Place samples in plastic specimen bag.
3. Place 2 inches depth of packing material in a Styrofoam box.
4. Place the sealed plastic specimen bag on top of packing material.
5. Place 5 pounds of dry ice on top of specimen bag.
6. Fill Styrofoam container completely with packing material.
7. Seal box and select an overnight courier for shipment.
8. Place a "dry ice" and 2 IATA Biological Materials label (opposing sides) on the side of the box.
9. Attach an appropriate shipping label.
10. Indicate the amount of dry ice in kg on the label (5 lb dry ice = 2.5 kg).
11. Schedule courier for pick-up. DO NOT ship samples on Friday without prior consent from the PGx vendor. Samples should be shipped via an overnight carrier to arrive the next morning. Prior to shipment, fax the Shipment Notification Form to the PGx vendor Study Manager as indicated in the Statement of Work.

7.4.2.2. Genomic or Genetic Analysis Endpoint(s)

Not applicable.

7.4.2.3. Disclosure of the Results of Genomic or Genetic Analysis

Because the nature and value of future PGx research cannot be known at this time, any results obtained from research involving PGx samples will not be disclosed to the patient or Investigators now or in the future.

7.4.2.4. Storage and Disposal of Specimens for Genomic or Genetic Banking and Analysis

Samples will be retained until exhausted or until the Sponsor requests destruction.

If the patient withdraws consent, the banked blood specimens will be promptly managed regarding proper disposition. However, the data will not be discarded if genetic analysis has been completed before the patient withdraws consent. For screen failures, PGx samples will be destroyed post CYP2C9 analysis.

8. EFFICACY ASSESSMENTS

Patients will be assessed for the efficacy endpoints listed in Section 2.3.

8.1. Primary Efficacy Endpoint

The primary efficacy endpoint will be ORR, defined as the proportion of patients who achieve a confirmed complete response (CR) or PR based on locally read tumor assessments according to RECIST 1.1 or other applicable assessment of treatment response based upon the applicable tumor. TGCT tumors should be assessed by MRI.

The RECIST 1.1 response categories are defined by the following criteria:

- **Complete Response** — Disappearance of all tumors.
- **Partial Response** — At least a 30% decrease in the sum of diameters of target tumors, taking as reference the baseline sum diameters.
- **Progressive Disease** — At least a 20% increase in the sum of diameters of target tumors, using the smallest sum on study as the reference. In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. The appearance of one or more new tumors is also considered progression.
- **Stable Disease** — Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for progressive disease (PD).

Complete and PR will define response for the primary endpoint and additional efficacy analyses. Determination of an overall response for each time point is based on the combination of responses for target lesions, and the presence or absence of one or more new lesions, in alignment with RECIST 1.1.

8.2. Secondary Efficacy Endpoint

The following evaluations comprise the secondary endpoints based upon the locally read tumor assessments:

- Duration of response (CR or PR) based on RECIST 1.1
- Time to progression (for TGCT and other non-malignant tumors)
- Progression-free survival (for malignant tumors)

8.3. Appropriateness of Selected Efficacy Endpoints

The selected efficacy endpoints are commonly used and widely accepted endpoints appropriate for the efficacy evaluation of investigational treatments in patients with these tumors.

9. SAFETY EVALUATION AND REPORTING

9.1. Adverse Event Collection and Reporting

All AEs (see Section 9.4.1 for definitions) occurring after the patient signs the ICF and through the posttreatment visit (28 d ± 7 d after the last dose of study drug), whether observed by the Investigator or reported by the patient, 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 medical history.

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

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

At each visit, the Investigator will determine whether any AEs have occurred by evaluating the patient. Adverse events may be directly observed, reported spontaneously by the patient, or by questioning the patient at each study visit. Patients 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. The Investigator's assessment must be clearly documented in the site's source documentation with the Investigator's signature.

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

For events that are serious due to hospitalization, the reason for hospitalization must be reported as the SAE (diagnosis or symptom requiring hospitalization). A procedure is not an AE or SAE, but the reason for the procedure may be an AE or SAE. Preplanned (prior to signing the ICF) procedures or treatments requiring hospitalization for preexisting conditions that do not worsen in severity should not be reported as SAEs (see Section 9.4.2 for definitions). For deaths, the underlying or immediate cause of death should always be reported as an SAE.

Disease progression is a study endpoint and, consequently, should not be reported as an AE/SAE. However, when a patient dies from disease progression with no other immediate causes, "disease progression" should be reported as an SAE. In addition, any serious untoward event that may occur subsequent to the reporting period that the Investigator assesses as related to study drug should also be reported and managed as an SAE.

The Investigator should follow patients with AEs until the event has resolved or the condition has stabilized. In case of unresolved AEs, including significant abnormal laboratory values at the end of study assessment, the events will be followed up until resolution or until they become clinically not relevant.

9.2. Safety Endpoint Events

Safety endpoints include physical examination, vital signs, 12-lead ECG, AE reports, serum chemistry, hematology, coagulation tests, urinalysis, and concomitant medications. All AEs will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 4.0.

9.3. Adverse Events of Special Interest

9.3.1. Combined Elevation 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 (ALT or AST $\geq 3 \times$ ULN with simultaneous TBil $\geq 2 \times$ ULN) should always be reported to Daiichi Sankyo Inc. using a Serious Adverse Event Report (SAVER) Form or a special collection in the 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 patient discontinues the study drug due to liver enzyme abnormalities, the patient will have additional clinical and laboratory evaluations as described in Section 5.4 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 patient administered a pharmaceutical product and that does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal clinical laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product (ICH E2A Guideline. Clinical Safety Data Management: Definitions and Standards for Expedited Reporting, Oct 1994).

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

9.4.2. Serious Adverse Event

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

- Results in death
- Is life-threatening

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

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

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

Note:

- Procedures are not AEs or SAEs, but the reason for the procedure may be an AE or SAE.
- Pre-planned (prior to signing the ICF) procedures or treatments requiring hospitalizations for pre-existing conditions that do not worsen in severity are not SAEs.

9.4.3. Grade Assessment

All AEs will be graded (1 to 5; see below) according to the latest NCI-CTCAE, for each episode.

- Grade 1: Mild – awareness of sign or symptom, but easily tolerated, ie, does not interfere with patient'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 patient's usual function
- Grade 4: Life-threatening or disabling AE – urgent intervention indicated
- Grade 5: Death related to AE

The NCI-CTCAE guidelines do not allow certain grades for certain AEs. For example, pain can be Grade 1 to 3 only (ie, cannot be life-threatening or fatal), whereas sepsis can only be Grade 4 or 5 (ie, can only be life-threatening or fatal). In addition, alopecia can only be Grade 1 or 2. The NCI-CTCAE guidelines should be followed closely.

Severity vs. 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 patient/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 grade 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 study drug administration, and cannot be reasonably explained by the patient's clinical state or other factors (eg, disease under study, concurrent diseases, and concomitant medications).

    or
  - The AE follows a reasonable temporal sequence from study drug administration, and is a known reaction to the drug under study or its chemical group, or is predicted by known pharmacology.
- Not related:
  - The AE does not follow a reasonable sequence from study drug administration, or can be reasonably explained by the patient's clinical state or other factors (eg, disease under study, concurrent diseases, and concomitant medications).

9.4.5. Action Taken Regarding Study Drug(s)

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

9.4.6. Other Action Taken for Event

- None
  - No treatment was required.
- Medication required
  - Prescription and/or OTC medication was required to treat the AE.
- Hospitalization or prolongation of hospitalization required
  - Hospitalization was required or prolonged because of the AE, whether or not medication was required.
- Other

9.4.7. Adverse Event Outcome

- Recovered/Resolved
  - The patient 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.
  - Document 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, SAEs, and events of special interest will be reported in the eCRF.

The following types of events should be reported by the Investigator on the SAE (SAVER) form 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 TBil $\geq 2 \times$ ULN); potential Hy's Law case), both serious and nonserious

All events (serious and nonserious) 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 Daiichi Sankyo Inc. for SAE reporting purpose.

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

See Section 15.10.5 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/Ethics Committee

Daiichi Sankyo Inc. and/or designee will inform Investigators, IRBs/IECs, and regulatory authorities of any suspected unexpected serious adverse reactions (SUSARs) occurring in other study sites or other Daiichi Sankyo Inc. studies of the investigational product, as appropriate per local reporting requirements. Daiichi Sankyo Inc. and/or designee will comply with any additional local safety reporting requirements.

In China, upon receipt of Daiichi Sankyo Inc.'s notification of SUSARs that occurred with the investigational product, unless delegated to Daiichi Sankyo Inc., it is the Investigator's responsibility to inform the IRB according to reporting guideline of the IRBs.

9.7. Exposure in Utero During Clinical Studies

Daiichi Sankyo Inc. must be notified of any female patient or any male patient whose female partner becomes pregnant while receiving or within 90 d of discontinuing the study drug. Reporting after follow-up visit or early termination is done voluntarily by the Investigator.

Although pregnancy is not technically an AE, all pregnancies must be followed to conclusion to determine their outcome. This information is important for both drug safety and public health concerns. It is the responsibility of the Investigator or designee to report any pregnancy in a female patient or a male patient's female partner using the Exposure In Utero (EIU) Reporting Form. Please contact your study monitor to receive the EIU Reporting Form upon learning of a pregnancy. The Investigator should make every effort to follow the patient until completion of the pregnancy and complete the EIU Reporting Form with complete pregnancy outcome information, including normal delivery and induced abortion. Any adverse pregnancy outcome, either serious or nonserious, should be reported in accordance with study procedures. If the outcome of pregnancy meets the criteria for immediate classification as an 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. For reports of pregnancy in the female partner of a male patient, the EIU Reporting Form (or SAE form if associated with an adverse outcome) should be completed with the patient's enrollment number, initials, and date of birth, and details regarding the female partner should be entered in the narrative section.

9.8. Clinical Laboratory Evaluations

Clinical laboratory evaluations will be performed by local laboratories at the study visits indicated in the Schedule of Events. For laboratory parameters, the reference range of the institution that performs the measurement will be used.

Clinical laboratory evaluations will be performed as outlined below.

Blood samples for analysis of the following clinical chemistry, hematologic, and coagulation parameters will be obtained:

Clinical Chemistry

Sodium	Total protein
Potassium	Albumin
Chloride	Triglycerides*
CO_2	Total cholesterol*
Calcium	HDL-cholesterol*
Phosphorus	LDL-cholesterol*
Glucose*	Uric acid
Blood urea nitrogen	Lactate dehydrogenase
Creatinine	

CO_2 = carbon dioxide; HDL = high-density lipoprotein; LDL = low-density lipoprotein.
* Fasting is recommended but not required.

Liver function tests as part of serum chemistry will be conducted on an at least weekly basis for the first 8 wk of pexidartinib treatment starting from the first dose in Part 1. After Week 8, the frequency of liver function tests will be reduced to once every 2 wk through Cycle 3, followed by monthly. If any abnormality is detected in the liver function tests, then follow-up laboratory tests will be performed on a weekly basis. The frequency of follow-up liver function tests will be increased to twice weekly for all Grade 3 aminotransferase increases and for any grade aminotransferase increase associated with bilirubin increase. (No bilirubin increase is defined as any 1 or more of the following: TBil ≤ ULN, TBil <20% above baseline, or direct bilirubin < ULN).

Liver Function Tests

Alkaline phosphatase	Total bilirubin
AST	Direct bilirubin
ALT	GGT

ALT = alanine aminotransferase; AST = aspartate aminotransferase; GGT = gamma-glutamyl transferase.

Hematology

Red blood cell count	Hemoglobin
White blood cell count with differential	Hematocrit
Platelet count	

Hepatitis Panel

Hepatitis B virus surface antigen test and HCV antibody test.

Coagulation

Prothrombin time, activated partial thromboplastin time, and INR.

Hormone Tests

Follicle-stimulating hormone will be measured for women of non-childbearing potential only.

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
Nitrites	

*Microscopic analysis required only in the event the dipstick is abnormal.

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 any invasive procedures, eg, blood withdraws. Vital signs and weight will be measured at the study visits mentioned in the Schedule of Events. Height will be measured at the Screening visit only.

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

Information will be entered in the eCRF on whether or not measured, date of measurement, and measurement results.

9.10. Electrocardiograms

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

Patients should rest in the supine position for at least 5 min before the ECG recording is started. The ECG recordings must be performed using a standard high-quality and high-fidelity electrocardiography machine equipped with computer-based interval measurements. For safety monitoring purposes, the ECGs should be reviewed, signed,

and dated promptly by a qualified Investigator (or Investigator's assistant or nurse practitioner) and any clinically important finding must be recorded on the appropriate eCRF. The Investigator is responsible for interpreting all ECGs. The results will include heart rate, RR interval, PR interval, QRS interval, QT interval, and QTcF interval.

At the visits when ECGs are to be performed, patients should be told to NOT take the morning dose of study drug; instead, they should be told to bring their bottle of study drug to the site and take the morning dose upon instruction by the site staff.

Whether or not measurement is performed, date performed, results, and findings for the parameters will be recorded in the eCRF.

9.11. Physical Examinations

The examination will be performed by a qualified individual such as the Investigator at the study visits indicated in the Schedule of Events.

Physical examination findings will be used to evaluate the following systems or areas: general appearance, oral cavity and neck, cardiothoracic, dermatologic, abdominal, musculoskeletal, and neurological.

9.12. Other Examinations

9.12.1. Pregnancy Test

For women 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.

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

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

10. OTHER ASSESSMENTS

Patients will be assessed for the efficacy endpoints and endpoints listed in Section 2.3.

10.1. Tumor Assessment

- Patients with TGCT – Noncontrast MRI of the affected joint will be performed at the study visits indicated in the Schedule of Events. Local evaluation of radiological response, SD or PD according to RECIST 1.1 will be recorded in the eCRF. The frequency of tumor assessments after Cycle 4 can be reduced if clinically appropriate and agreed with the Sponsor Medical Monitor.
- Patients with other tumors – The response of the tumor to study treatment should be assessed using a standard procedure applicable to the patients' tumor, eg, MRI, CT, or other. The same procedure should be used throughout the study. The frequency of tumor assessments after Cycle 4 can be reduced if clinically appropriate and agreed with the Sponsor Medical Monitor.

11. STATISTICAL METHODS

11.1. General Statistical Considerations

The data cutoff for the primary PK analysis will occur after all patients have either discontinued or completed the last Part 1 assessments. The data cutoff for the primary efficacy and safety analyses will occur after all patients have either discontinued the study or completed the end of C7D1 assessments.

Continuous variables will be summarized by the number of observations, mean, standard deviation, median, 25th and 75th percentile, and minimum and maximum values. Categorical variables will be summarized using frequency counts and percentages.

Assessments of change from baseline to posttreatment or the ratio of posttreatment to baseline will include only those patients with both baseline and posttreatment 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.

When the number of patients with a particular tumor is at least 4, the baseline efficacy and safety parameters will be summarized and calculated for that tumor in addition to the overall result.

11.2. Analysis Sets

11.2.1. Enrolled Analysis Set

The Enrolled Analysis Set will include all patients who sign the ICF and are enrolled in the study.

11.2.2. Full Analysis Set/Safety Analysis Set

The Full Analysis Set (FAS)/Safety Analysis Set will include all patients who received at least 1 dose of pexidartinib.

11.2.3. Per-Protocol Analysis Set

Not applicable.

11.2.4. Pharmacokinetic Analysis Set

The PK Analysis Set will include all patients in the Enrolled Analysis Set who received at least 1 dose of study drug (pexidartinib, midazolam, or S-warfarin) and had measurable plasma concentrations of pexidartinib or midazolam and S-warfarin.

11.3. Procedures for Handling Missing, Unused, and Spurious Data

For the primary efficacy analysis as well as for all analyses of responder proportion endpoints performed on the FAS, patients who do not provide data for the responder endpoint will be considered nonresponders, ie, assigned to the less favorable outcome for the endpoint.

11.4. Study Population Data

Patient disposition will be summarized for patients in the Enrolled Analysis Set. The total number of patients for each defined analysis population will also be tabulated. The demographic and baseline characteristics will be summarized descriptively for the FAS/Safety Analysis Sets. Study drug exposure and study duration will be summarized using descriptive statistics for the Safety Analysis Set.

Continuous demographic variables (age [calculated from the date of birth to the date when the ICF was signed], weight, height, and body mass index) for all patients will be summarized with descriptive statistics. Categorical demographic variables (sex, race, and ethnicity) will be summarized with frequency counts and corresponding percentages. Medical/Surgical history data, physical examination data, and prior/concomitant medications will be listed.

11.5. Statistical Analysis

11.5.1. Pharmacokinetics and Exposure-Response Analyses

11.5.1.1. Noncompartmental Pharmacokinetic Analysis

The PK analyses will be performed on the PK Analysis Set. Plasma-concentration time data for S-warfarin, midazolam, 5-hydroxy midazolam, pexidartinib, and ZAAD-1006a will be summarized by visit and time using descriptive statistics and graphically.

An analysis of variance (ANOVA) model with treatment as fixed effects, and patient as random effect will be used to compare natural-log transformed PK parameters (Cmax and AUClast) of the substrates with and without the co-administration of pexidartinib. The combination treatments (pexidartinib + substrate) will be the test and substrate alone will be the reference for the comparison in regards to each substrate. Geometric mean ratios and their corresponding 90% confidence intervals (CI) between the treatments will be calculated by anti-log transformation. Time to reach maximum plasma concentration will be analyzed using a nonparametric method. The point estimate of the treatment difference and the corresponding 95% confidence intervals will be calculated and anti-logged to obtain the point estimate and 95% CI on the linear scale for the ratio of geometric means of the test as compared with the reference.

No DDI will be concluded if the 90% CI of the ratio of the test to the reference completely remains within 80-125%.

11.5.2. Efficacy Analyses

11.5.2.1. Primary Efficacy Analysis

The primary efficacy endpoint is the proportion of patients who achieve a CR or PR based on local tumor assessments (see Section 8). The primary analysis will be completed using the FAS. The estimate of the proportion and two sided 95% CI based on Clopper Pearson method will be provided. The ORRs will also be calculated.

11.5.2.2. Secondary Efficacy Analyses

The efficacy endpoints to be calculated and summarized include:

- Duration of response
- Time to progression (for TGCT and other non-malignant tumors)
- Progression-free survival (for malignant tumors)

Duration of response will be analyzed as a secondary endpoint and will be summarized for responders based on RECIST 1.1. Duration of response is defined from the date of the first recorded response to the first date of documented disease progression. For patients who do not have radiological progression, the duration will be censored at the date of the last tumor assessment. The Kaplan-Meier product limit method will be used to compute the estimate and 95% CI of the median and 25^{th} and 75^{th} percentiles. The number of responders, the number with subsequent disease progression, and the number with censored values will be displayed as well. Within the framework of Kaplan-Meier methodology, the estimates for proportions of responders with response durations longer than 3, 6, 12, 18, and 24 mo will also be provided.

11.5.3. Pharmacodynamic Analyses

Optional blood samples collected at the discretion of the Investigator/patient at specified time points may be analyzed for PDy biomarkers. No formal statistical analysis of PDy endpoints will be performed. Pharmacodynamic data from each assay will be listed. Biomarker data will be summarized by visit using descriptive statistics.

11.5.4. Safety Analyses

The analyses of safety will be performed on the Safety Analysis Set. The summary and display of TEAEs will be performed.

Terminology of the Medical Dictionary for Regulatory Activities (MedDRA) will be used to assign system organ class (SOC) and preferred term (PT) classification to AEs and diseases, based on the original terms entered in the eCRF.

The incidence of TEAEs will be summarized by SOC, PT, relationship to the study drug, and severity for each treatment group. A by-patient listing will be provided for those patients who experience an SAE, including death, or experience an AE associated with early withdrawal from the study or study drug.

11.5.4.1. Adverse Event Analyses

Treatment-emergent adverse events are AEs that occur, having been absent before the first dose of study drug, or worsen in severity after initiating the study drug. Treatment-emergent adverse events will be coded using MedDRA and assigned grades based on version 4.0 of the NCI-CTCAE. The number and percentage of patients reporting TEAEs will be tabulated by the worst CTCAE grade, SOC, and PT. Similarly, the number and percentage of patients reporting treatment-emergent SAEs will be tabulated, as well as TEAEs leading to discontinuation of study drug.

A by-patient AE (including treatment-emergent) data listing including but not limited to verbatim term, SOC, PT, CTCAE grade, and relationship to study drug will be provided. Deaths, other SAEs, and other significant AEs, including those leading to discontinuation of study drug, will be listed.

11.5.4.2. Clinical Laboratory Evaluation Analyses

Descriptive statistics will be provided for the clinical laboratory results by scheduled time of evaluation for the Safety Analysis Set, as well as for the change from baseline. In addition, mean change from baseline will be summarized for the maximum and minimum posttreatment values and the values at the end of treatment visit.

Abnormal clinical laboratory results will be graded according to NCI-CTCAE version 4.0, if applicable, and the grade will be presented in a by-patient data listing. A shift table, presenting the 2-way frequency tabulation for baseline and the worst posttreatment value according to the NCI-CTCAE grade, will be provided for clinical laboratory tests.

Abnormal clinical laboratory test results deemed of clinical significance or of Grade 3 or 4 will be listed.

11.5.4.3. Vital Sign Analyses

Descriptive statistics will be provided for the vital signs measurements by scheduled time of evaluation for the Safety Analysis Set, as well as for the change from baseline. In addition, mean change from baseline will be presented by treatment group for the maximum and minimum posttreatment values and the values at the end of treatment visit.

11.5.4.4. Electrocardiogram Analyses

Descriptive statistics will be provided for the ECG measurements by scheduled time of evaluation for the Safety Analysis Set, as well as for the change from baseline. In addition, the number and percentage of patients with ECG interval values meeting the criteria will be tabulated (eg, QTcF $\leq$ 450 ms, > 450 to $\leq$ 480 ms, > 480 ms to $\leq$ 500 ms, and > 500 ms) and QTcF maximum changes from baseline (> 30 and > 60 ms) over all posttreatment evaluations will be summarized. Electrocardiogram data will also be presented in the data listings.

11.5.4.5. Physical Examination Analyses

Physical examination data will be listed.

11.5.4.6. Concomitant Medication Analyses

Concomitant medications will be coded using the World Health Organization drug dictionary (most recent version). Number and percentage of patients taking concomitant medications will be summarized for the Safety Analysis Set.

11.5.4.7. Other Analysis

Results for pharmacogenomics, pharmacodynamics, and biomarker analyses will be listed.

11.6. Interim Analysis

Preliminary PK analysis will be done with approximately 12 patients and if deemed adequate will proceed with a data snapshot and formal analysis.

11.7. Sample Size Determination

Approximately 30 patients are planned to be enrolled to achieve 24 patients evaluable for DDI. The sample size is not based on statistical hypothesis testing, but a sample size of 24 patients will provide a certain magnitude of precision for DDI evaluation.

- Assuming an intrapatient coefficient of variation for AUC of 22% for S-warfarin (estimated from ARQ 197-A-U158), and assuming pexidartinib had no or only minor effect (ratio <1.05) on S-warfarin PK, a sample size of 24 patients was required to provide at least 80% power to conclude the absence of effect of pexidartinib on AUClast of S-warfarin, using the criteria of 90% CI within 80% to 125% no effect boundaries.
- Assuming an intrapatient coefficient of variation for AUC of 42% for midazolam (estimated from ARQ 197-A-U158), Table 11.1 shows expected 95% confidence intervals of AUC ratio will be available for DDI evaluation with a sample size of 24 patients under an intrapatient coefficient of variation of 40% and 50%.

Table 11.1: 95% Confidence Intervals by Ratio and Intra-Patient Coefficient of Variation of Area Under the Plasma Concentration-Time Curve (N=24)

Ratio of AUC	Intra-patient coefficient of variation			
	40%		50%	
	Lower bound	Upper bound	Lower bound	Upper bound
1.0	0.79	1.27	0.74	1.35
1.2	0.95	1.52	0.89	1.62
1.4	1.10	1.78	1.04	1.89
1.6	1.26	2.03	1.19	2.16
1.8	1.42	2.29	1.34	2.43
2.0	1.58	2.54	1.48	2.70

AUC = area under the plasma concentration-time curve.

11.8. Statistical Analysis Process

The clinical study will be analyzed by Daiichi Sankyo Inc. or its agent/CRO following this protocol and Statistical Analysis Plan (SAP), which will demonstrate all methodologies and displays/shells for statistical analyses.

The SAP will provide the statistical methods and definitions for the analysis of the efficacy and safety data, as well as describe the approaches to be taken for summarizing other clinical study information such as patient 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.

All statistical analyses will be performed using SAS® Version 9.2 or higher (SAS Institute, Cary, NC 27513).

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 the 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

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

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

The monitor will communicate to the Investigator any deviations from the protocol, Standard Operating Procedures, GCP, and applicable regulations and will ensure that appropriate action(s) designed to prevent recurrence of the detected deviations is taken and documented. The site will keep a running log of all protocol deviations.

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

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

12.2. Data Collection

Daiichi Sankyo Inc. or its designee will provide the study sites with secure access to and training on the Electronic Data Capture (EDC) application, sufficient to permit site personnel to enter or correct information in the eCRFs for the patients for which they are responsible.

eCRFs will be completed for each study patient. It is the Investigator's responsibility to ensure the accuracy, completeness, clarity, and timeliness of the data reported in the patient's eCRF.

The Investigator, or designated representative, should complete the eCRF as specified in the eCRF Completion Guidelines.

The audit trail entry will show the user's identification information, and the date and time of the correction. The Investigator must provide through the EDC application formal approval of all the information in the eCRFs and changes to the eCRFs to endorse the final submitted data for the patient for which he or she is responsible.

Daiichi Sankyo Inc. or a designee will retain the eCRF data and corresponding audit trails. A copy of the final archival eCRF in the form of a compact disk or other electronic media will be placed in the Trial Master file.

12.3. Data Management

Each patient will be identified in the database by a unique patient identifier as defined by Daiichi Sankyo Inc.

To ensure the quality of clinical data across all patients and sites, a clinical data management review will be performed on patient data according to specifications given by Daiichi Sankyo Inc. or designee. Data will be vetted both electronically and manually for eCRFs, and the data will be electronically vetted by programmed data rules within the application. Queries generated by rules and raised by reviewers will be generated within the EDC application. During this review, patient data will be checked for consistency, omissions, and any apparent discrepancies.

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

Serious adverse events in the clinical database will be reconciled with the safety database. All AEs will be coded using MedDRA.

12.4. Study Documentation and Storage

Source documents are original documents, data, and records from which the patient'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. eCRF entries may be considered source data if the eCRF is the site of the original recording (ie, there is no other written or electronic record of data).

Records of patients' 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 Daiichi Sankyo Inc. 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, Daiichi Sankyo Inc. 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. The Trial Master File includes:

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

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

Patient'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 Daiichi Sankyo Inc. 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 Daiichi Sankyo Inc. 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 principal Investigator and/or institution will sign a clinical study agreement with Daiichi Sankyo Inc./CRO. This agreement will include the financial information agreed upon by the parties.

13.2. Reimbursement, Indemnity, and Insurance

Daiichi Sankyo Inc. provides insurance for study patients 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 y after the study has ended, whichever occurs first. Therefore, the study site will have the opportunity to publish the results of the study, provided that Daiichi Sankyo Inc. has had the opportunity to review and comment on the study site's proposed publication prior to it being submitted for publication with the prior advice of Legal Affairs (intellectual property council) and with proper regard to the protection of patients' identities.

15. ETHICS AND STUDY ADMINISTRATIVE INFORMATION

15.1. Compliance Statement, Ethics and Regulatory Compliance

This study will be conducted in accordance with ethical principles founded in the Declaration of Helsinki and in compliance with the protocol, GCP, and applicable regulatory requirements (including ICH guidelines and applicable local regulatory requirements). The IRB/IEC will review all appropriate study documentation in order to safeguard the rights, safety, and well-being of the patients. The study will only be conducted at sites where IRB/IEC approval has been obtained. The protocol, IB, ICF, advertisements (if applicable), written information given to the patients (including diary cards and PRO instruments), safety updates, annual progress reports, and any revisions to these documents will be provided to the IRB/IEC by the Investigator or Daiichi Sankyo Inc., as allowable by local regulations.

15.2. Patient Confidentiality

The Investigators and Daiichi Sankyo Inc. will preserve the confidentiality of all patients taking part in the study, in accordance with GCP and local regulations.

The Investigator must ensure that the patient's anonymity is maintained on the eCRFs or other documents submitted to Daiichi Sankyo Inc. or the CRO; patients should be identified by a unique patient identifier as designated by Daiichi Sankyo Inc. Documents that are not for submission to Daiichi Sankyo Inc. or the CRO (eg, signed ICF) should be kept in strict confidence by the Investigator.

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

15.3. Informed Consent

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

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

The patient's written informed consent should be documented in the patient's medical records. The ICF should be signed and personally dated by the patient 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 patient. The date and time (if applicable) that informed consent was given should be recorded on the eCRF.

If the patient cannot read, then according to ICH GCP Guideline, Section 4.8.9, an impartial witness should be present during the entire informed consent discussion. This witness should sign the ICF after the patient has consented to the patient'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 patient and that informed consent was freely given by the patient.

Suggested model text for the ICF for the study and any applicable subparts (genomic, PK, etc.) are provided in the Daiichi Sankyo Inc.'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, patient ICF, IB, any written instructions to be given to the patient, available safety information, patient recruitment procedures (eg, advertisements), information about payments and compensation available to the patients, 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 Daiichi Sankyo Inc. 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 Daiichi Sankyo Inc. or CRO, in accordance with local procedures.

As required by local regulations, the Daiichi Sankyo Inc. 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 happens only after the approval by the relevant regulatory bodies.

In the event of any prohibition or restriction imposed (eg, clinical hold) by 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, Daiichi Sankyo Inc. should be informed immediately.

In addition, the Investigator will inform Daiichi Sankyo Inc. immediately of any urgent safety measures taken by the Investigator to protect the study patients 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 Daiichi Sankyo Inc. and, if required, by the regulatory authority(ies), and that was given approval/favorable opinion by the IRB/IEC.

A deviation to any protocol procedure, or a waiver to any stated criteria will not be allowed in this study except where necessary to eliminate immediate hazard(s) to the patient. Daiichi Sankyo Inc. 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 patient was ineligible or received the incorrect dose or investigational treatment and had at least one administration of the study drug, data should be collected for safety purposes, and the Daiichi Sankyo Inc.'s Medical Monitor or designee should be informed immediately.

The Investigator should notify the IRB/IEC 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 patients or the conduct of the study, the Sponsor will inform all Investigators involved in the clinical study, IRBs/ECs, and regulatory authorities of such information, and when needed, will amend the protocol and/or patient information.

The Investigator should immediately inform the patient whenever new information becomes available that may be relevant to the patient's consent or may influence the patient'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 patient is willing to remain in the study.

If the patient information is revised, it must be re-approved by the IRB/IEC. The Investigator should obtain written informed consent to continue participation with the revised written information even if patients were already informed of the relevant information. The Investigator or other responsible personnel who provided the explanations and the patient 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 Inc. or the CRO. Also, Daiichi Sankyo Inc. will ensure the timely submission of amendments to regulatory authorities.

A global protocol amendment will affect study conduct at all study sites in all regions of the world. 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 a particular study site(s) and/or in a particular region/country. Daiichi Sankyo Inc. approval of local amendments will be clearly documented.

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

15.8. Study Termination

The study may be terminated at any time by the IRB, Daiichi Sankyo Inc., or regulatory agencies as part of their duty is to ensure that the research patients are protected.

Daiichi Sankyo Inc. reserves the right to temporarily suspend or prematurely discontinue this study either at a single study site or at all study sites at any time for reasons including, but not limited to, safety or ethical issues or severe noncompliance. If Daiichi Sankyo Inc. determines such action is needed, then Daiichi Sankyo Inc. will discuss this with the Investigator (including the reasons for taking such action) at that time. When feasible, Daiichi Sankyo Inc. will provide prior notification to the Investigator of the impending action prior to its taking effect.

Daiichi Sankyo Inc. 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 Daiichi Sankyo Inc. In addition, arrangements will be made for return of all unused study drugs in accordance with Daiichi Sankyo Inc.'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 Daiichi Sankyo Inc.

15.9. Data and Safety Monitoring Board

Not applicable.

15.10. Address List

15.10.1. Sponsor's Clinical Study Leader

[redacted]
Execute Director, Clinical Development Oncology
Daiichi Sankyo Inc.
211 Mt Airy Road
Basking Ridge, NJ 07920-2311
[redacted]

15.10.2. Sponsor's Clinical Study Manager

[redacted]
Senior Clinical Study Manager, Clinical Development Operations
Daiichi Sankyo, Inc.
211 Mt Airy Road
Basking Ridge, NJ 07920-2311
[redacted]

15.10.3. Sponsor's Medical Monitor

[redacted]
Senior Director
Global Oncology R&D
Daiichi Sankyo, Inc.
211 Mt. Airy Road
Basking Ridge, NJ 07920-2311
[redacted]

15.10.4. Sponsor's Pharmacologist

[redacted]
Director, Translation Medicine and Clinical Pharmacology
Daiichi Sankyo Pharma Development
211 Mt. Airy Road
Basking Ridge, NJ 07920-2311
[redacted]

15.10.5. Sponsor's Safety Contacts

[redacted]
Senior Director, Clinical Safety and Pharmacovigilance
Daiichi Sankyo, Inc.
399 Thornall St.
Edison, NJ 08837
[redacted]

15.10.6. Contract Research Organizations

To Be Decided

15.10.7. Electronic Data Capture Vendor

Medidata Solutions, Inc.
350 Hudson Street
New York, NY 10014
[redacted]
www.mdsol.com

15.10.8. Interactive Web Response System Vendor

Not applicable

15.10.9. Bioanalytical Vendor

[redacted]
Celerion
621 Rose Street
Lincoln, NE 68502
USA
[redacted]

15.10.10. Pharmacogenomics Vendor

15.10.10.1. Pharmacogenomics Vendor (CYP2C9 Analysis)

[redacted]
Project Manager
Cancer Genetics, Inc.
133 Southcenter Court, Suite 400
Morrisville, NC 27560
[redacted]

15.10.10.2.Pharmacogenomics Vendor (Long-Term Storage)

[redacted]
Team Coordinator, Sample Management Operations
Biostorage Technologies, Inc
[redacted]

15.10.11. Central Laboratory
TBD

15.10.12. Sponsor's Biostatistician

[redacted]
211 Mt. Airy Road
Basking Ridge, NJ 07920-2311
[redacted]

15.10.13. Sponsor's East Regional Project Leader

[redacted]
Associate Director, Asia Development Department, R&D Division,
Daiichi Sankyo Co., Ltd
1-2-58, Hiromachi, Shinagawa-ku
[redacted]

15.10.14. Sponsor's Regional Contacts
Korea

[redacted]
County Project Leader, Clinical Development Team, Medical Department,
Daiichi Sankyo Korea Co., Ltd
19th Fl. SC Bank Bldg
47 Jong-ro, Jongno-gu,
Seoul, 03160, Korea

Taiwan

[redacted]
Senior Clinical Research Manager, Development & Medical Affairs Department,
Daiichi Sankyo Taiwan Ltd
[redacted]

16. REFERENCES

1. PLX3397 Investigator's Brochure, v.7.1. Berkeley, CA: Plexxikon Inc. Mar 2016.
2. Dumond JB, Vourvahis M, Rezk NL, Patterson KB, Tien HC, White N, et al. A phenotype-genotype approach to predicting CYP450 and P-glycoprotein drug interactions with the mixed inhibitor/inducer tipranavir/ritonavir. Clin Pharmacol Ther 2010;87(6):735-42.
3. Myers BW, Masi AT. Pigmented villonodular synovitis and tenosynovitis: a clinical epidemiologic study of 166 cases and literature review. Medicine. 1980;(59):223-38.
4. 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. APPENDICES

17.1. List of Common CYP3A4 Inhibitors and Inducers

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

17.2. Schedule of Events

17.2.1. Schedule of Assessments – Part 1

Events	Screening			Part 1 DDI Phase										
Study Day[a]	**≤ 21[b]**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**15**	**16**	**17**	**18**
Pexidartinib Cycle/Day		**n/a**	**n/a**	**n/a**	**n/a**	**C1D1[c]**	**C1D2**	**C1D3**	**C1D4**	**C1D5**	**C1D11**	**C1D12**	**C1D13**	**C1D14**
Visit Window						**+2d**				**+1d**	[d]			
Informed Consent	X													
Prior and Concomitant Medication	X													
Demographic Information	X													
Medical/Surgical History	X													
FSH Level[e]														
HIV/Hepatitis B, HCV														
Physical Examination	X	X				X					X			X[f]
Drug/Alcohol Screening	X													
Height	X													
Weight	X	X				X					X			
Tumor Assessment	X													
Coagulation Test	X													
Serum Chemistry, Hematology, and Coagulation	X	X[g]				X[g]				X[h]	X[h]			
Urinalysis	X													
Vital Signs[i]	X	X[k]				X[k]					X[k]			
12-lead ECG[j]	X	X[m]				X[m]					X[m]			
Pregnancy Test[l]	X													
Midazolam and S-warfarin Administration		X				X[o]					X[o]			
PK Sampling for Midazolam		X[n]	X[q]	X[r]		X[n]	X[q]	X[r]			X[n]	X[q]	X[r]	
PK Sampling for S-warfarin		X[n]	X[q]	X[r]	X[s]	X[n]	X[q]	X[r]	X[s]	X[t]	X[n]	X[q]	X[r]	X[s]
Pexidartinib Administration at Clinc[u]						X[o]	X	X	X	X	X[o]	X	X	X
Pexidartinib Dosing[v]						BID continuously								
PK Sampling for Pexidartinib						X[p]					X[p]			
Pexidartinib Dipsensation[w]						X	X	X	X	X	X	X	X	X
Pexidartinib Treatment Compliance							X[x]				X			
Optional Tumor Biopsy or Blood Sample for Pdy or Circulating Tumor DNA	X													
Pharmacogenomic Sampling	X	X												
Record of Concomitant Medication	X													
AE Reporting	X													

AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BID = twice daily; C#D# = cycle number, day number; DDI = drug-drug interaction; ECG = electrocardiogram; GGT = gamma-glutamyl transferase; HCV = Hepatitis C virus; HIV = human immunodeficiency virus; n/a = not applicable; PK = pharmacokinetic; TGCT = tenosynovial giant cell tumor.

a. Patients must arrive to the clinical site fasted (approximately 10 h) on Days 1, 5, and 15.

b. Screening will take place between Day -21 and Day -1. Patients may be rescreened.

c. Cycle and day of pexidartinib, where C1D1 is the first day of pexidartinib treatment in Part 1 and C1D9 is the 9th day of pexidartinib treatment. Pexidartinib treatment continues seamlessly from Part 1 into Part 2, where the first approximately 2 wk of treatment are given in Part 1. For the Day 5 visit, patients may delay visit up to 2 days, in which case the 96h samples should be collected on Day 5 or up to 1 d later.

d. May be delayed up to 1 d for patients with TGCT or up to 4 d for patients with malignant disease, if needed. This visit cannot be delayed by more than 1 d for patients with TGCT or other non-malignant tumor because they require a pexidartinib dose reduction to 800 mg/d after 14 d of treatment that cannot be completed before the last PK sample is taken. If the Part 1 Day 15 visit is delayed, pexidartinib BID administration and weekly safety assessments must continue (±1 d) despite the delay. The cycle day count begins from the first dose of pexidartinib (C1D1) and continues regardless of any delay.
e. For postmenopausal women only.
f. Or upon early withdrawal. The assessments can be done after the last PK draw on the final day of Part 1 DDI Phase.
g. Predose.
h. Predose. Alkaline phosphatase, ALT, AST, total and direct bilirubin, and GGT must be evaluated for the possible need to modify pexidartinib treatment before the patient leaves the clinic
i. Measured after patient has rested in the recumbent position at least 5 min.
j. Measured after patient has rested in the supine position at least 5 min.
k. Predose and 2 and 4 h postdose.
l. Women of childbearing potential only. Women who have been amenorrheic for ≥ 12 mo due to medical reasons other than sterilization will be regarded as women of childbearing potential.
m. Predose.
n. Predose and 0.5, 1, 2, 3, 4, 6, 8, and 10 h postdose (±10 min up to 1 h, ±10% thereafter).
o. Coadminister midazolam, S-warfarin (with Vitamin K), and pexidartinib.
p. Collect sample for pexidartinib and ZAAD-1006a predose and 0.5, 1, 1.5, 2, 3, 4, 6, 8, and 10 (±1) h postdose.
q. 24 (±10%) h postdose.
r. 48 (±10%) h postdose.
s. 72 (±2) h postdose.
t. 96 (±2) h postdose.
u. Patients must be administered the morning dose of pexidartinib at the clinic on Days 5 and 15, and the evening dose may be administered optionally at the clinic on these days. On other days with a clinic visit, the morning dose is preferably administered in the clinic, in which case patients will be instructed not to take pexidartinib in the morning at home on these days. Otherwise, pexidartinib is taken outside the clinic.
v. Pexidartinib will be taken BID from Day 5 onwards. Patients will be instructed to take 2 capsules (400 mg/d) in the morning and 3 capsules (600 mg/d) in the evening (total 1000 mg/d). Patients are to be fasted 1 h before dosing and continue fasting 2 h after dosing. The dose of pexidartinib will decrease to 800 mg/d (400 mg BID) after 14 d of treatment for patients with TGCT or other non-malignant tumor. Patients will be instructed to not take study drug at home on days when pexidartinib will be administered at the clinical site. Pexidartinib may need to be interrupted or the dose reduced or discontinued depending upon tolerance.
w. Patients will be dispensed only enough pexidartinib to reach the next study visit.
x. If applicable.

17.2.2. Schedule of Assessments – Part 2

Events	Part 2 Pexidartinib Extension Phase										Post Tx
Study Day	**19**	**26**	**33**	**40**	**47**	**54**	**61**	**75**	**89**	**n/a**	**n/a**
Pexidartinib Cycle/Day	**C1D15**	**C1D22**	**C2D1**	**C2D8**	**C2D15**	**C2D22**	**C3D1**	**C3D15**	**C4D1**	**C5+D1[a]**	**28 days**
Visit Window	**+1d**	**±2d**	**±2d**	**±2d**	**±2d**	**±2d**	**±2d**	**±7d**	**±7d**	**±7d**	**±7d**
Physical Examination			X						X	Q2 cycles	X
Tumor Assessment							X			Q2 cycles[b]	
Serum Chemistry/Hematology[c]	X	X	X	X	X	X	X	X	X	X	X
Urinalysis	X										X
Vital Signs[d]	X		X				X		X	X	X
12-Lead Ecg[e]	X										X
Pregnancy Test[f]			X				X		X	X	X
PK Sampling for S-Warfarin	X[g]										
Pexidartinib Dosing[h]	BID continuously										
Pexidartinib Dipsensation[i]	X	X	X	X	X	X	X	X	X	X	
Pexidartinib Treatment Compliance	X										
Optional Tumor Biopsy or Blood Sample for Pdy or Circulating Tumor DNA			X						X		
Record of Concomitant Medication	X										
AE Reporting	X										

AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BID = twice daily; C#D# = cycle number, day number; ECG = electrocardiogram; GGT = gamma-glutamyl transferase; n/a = not applicable; PDy = pharmacodynamics; PK = pharmacokinetic; Q = every; TGCT = tenosynovial giant cell tumor; Tx = treatment.

a. The 28-d treatment cycles will continue until there is no longer any clinical benefit or until other reasons for discontinuation are met.
b. May be reduced after Cycle 4 if clinically appropriate and agreed upon by the Sponsor's Medical Monitor.
c. Predose. Alkaline phosphatase, ALT, AST, total and direct bilirubin, and GGT must be evaluated for the possible need to modify pexidartinib treatment before the patient leaves the study center (except Post Tx visit). More frequent assessments may be required in the case of abnormalities as defined in the protocol.
d. Measured after patient has rested in the recumbent position at least 5 min.
e. Measured after the patient has rested in the supine position at least 5 min.
f. Women of childbearing potential only. Women who have been amenorrheic for ≥ 12 mo due to medical reasons other than sterilization will be regarded as women of childbearing potential.
g. 96 (±2) h postdose.
h. The dose of pexidartinib will decrease to 800 mg/d (400 mg BID) after 14 d of treatment for patients with TGCT or other non-malignant tumors.
i. Pexidartinib will be taken BID. Patients will be instructed to take 2 capsules (4000 mg/d) in the morning and 3 capsules (6000 mg/d) in the evening (total 1000 mg/d). The dose of pexidartinib will be 800 mg/d (400 mg BID) for patients with TGCT or other non-malignant tumor. Pexidartinib may need to be interrupted or the dose reduced or discontinued depending upon tolerance.