CLINICAL STUDY PROTOCOL

MULTICENTER, SINGLE ARM STUDY OF THE EFFICACY AND SAFETY OF PEXIDARTINIB IN ADULT SUBJECTS WITH TENOSYNOVIAL GIANT CELL TUMOR

PL3397-A-A303

VERSION 4.0, 29 JAN 2021

VERSION 3.0, 25 FEB 2020

VERSION 2.0, 25 NOV 2019

VERSION 1.1, 31 MAY 2017

VERSION 1.0, 20 MAY 2016

DAIICHI SANKYO

INVESTIGATOR AGREEMENT

Sponsor Approval:

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

PPD	PPD
Print Name	**Signature**
Clinical study team lead	29 Jan 2021
Title	**(DD MMM YYYY)**

Investigator's Signature:

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

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

I agree to conduct this study according to this protocol and to comply with its requirements, subject to ethical and safety considerations and guidelines, and to conduct the study in accordance with the Declaration of Helsinki, International Conference on Harmonisation guidelines on Good Clinical Practice (ICH E6), and applicable regional regulatory requirements.

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

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

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

PROTOCOL SYNOPSIS

Protocol Number:	PL3397-A-A303
Investigational Product:	Pexidartinib (PLX3397)
Active Ingredient/INN:	Pexidartinib (PLX3397)
Study Title:	Multicenter, single arm study of the efficacy and safety of pexidartinib in adult subjects with tenosynovial giant cell tumor
Study Phase:	Phase 3
Indication Under Investigation:	The treatment of adult patients with symptomatic TGCT associated with severe morbidity or functional limitations and not amenable to improvement with surgery.
Study Objectives:	Primary Objective: To evaluate the efficacy in the Asian patients with TGCT by determining the overall response rate (ORR) of pexidartinib based on Response Evaluation Criteria in Solid Tumors, version 1.1 (RECIST 1.1) at Week 25 by centrally reviewed magnetic resonance imaging (MRI) scan. Secondary Objectives: To evaluate: • Response of pexidartinib based on Tumor Volume Score (TVS) at Week 25 by centrally reviewed MRI scan • Range of motion at Week 25 • Patient-Reported Outcomes Measurement Information System (PROMIS) Physical Function Scale at Week 25 • Best overall response of pexidartinib based on RECIST 1.1 and TVS by centrally reviewed MRI scan • Duration of response of pexidartinib based on RECIST 1.1 and TVS by centrally reviewed MRI scan • Safety

	• Pharmacokinetics (PK) Exploratory Objectives: To evaluate: • ORR of pexidartinib based on RECIST 1.1 at Week 25 by locally reviewed MRI scan • ORR of pexidartinib based on modified RECIST 1.1-sum of the short-axis dimension (SSD) at Week 25 by centrally reviewed MRI scan • EuroQol five-dimensional descriptive system (EQ-5D-5L) • Best overall response of pexidartinib based on RECIST 1.1 by locally reviewed MRI scan • Duration of response of pexidartinib based on RECIST 1.1 by locally reviewed MRI scan • Duration of response of pexidartinib based on modified RECIST 1.1-SSD by centrally reviewed MRI scan • Photographic documentation of tumor size change • Results of the Surgical Assessment Questionnaire • Pharmacodynamics (PDy) • Long term follow-up of the subject status after the end-of-study or early termination visit
Study Design:	This is a multicenter, single arm study of pexidartinib orally administrated in adult subjects with symptomatic TGCT associated with severe morbidity or functional limitations and not amenable to improvement with surgery. Subjects who sign the Informed Consent Form (ICF) and meet the eligibility criteria can be enrolled in the study. Subjects will take 400 mg twice daily for a total daily dose of 800 mg. Pexidartinib will be administered continuously with 28-day treatment cycle until criteria for discontinuation are reached. The subjects who complete primary endpoint assessments (ie, complete 24 weeks of dosing and the Week 25 assessments including MRI) will be eligible to continue receiving pexidartinib until disease

	progression, unacceptable toxicity, the occurrence of other termination criteria, or withdrawal from the study. Primary, secondary, exploratory endpoints will be assessed during the study according to the schedule of events. Any disease progression before Week 25 must be verified by a central MRI reading. If a central reading confirms RECIST 1.1 defined disease progression, then the subject will be discontinued from the study unless the Investigator and Daiichi Sankyo's Medical Monitor judge that the subject would potentially benefit from continued treatment with pexidartinib. After completion of the end-of-study or early termination visit, subject status will be collected every 6 months as a long term follow-up at least 2 years.
Study Duration:	Each subject will spend a maximum of 6 weeks in screening. All subjects will continue in the study until disease progression, unacceptable toxicity, or any of the other termination criteria. Primary analysis will be performed after the last subject completes the Week 25 assessments. The duration after the Week 25 assessments will vary among subjects, as this portion of the study will continue until all subjects have either completed the study drug or withdrawn from the study.
Study Sites and Location:	Approximately 10 to 15 study sites in China and Taiwan
Subject Eligibility Criteria:	<u>Inclusion Criteria:</u> Subjects must satisfy all of the following criteria to be included in the study: 1. Age ≥ 18 years (Age ≥ 20 years in Taiwan). 2. A diagnosis of TGCT (i) that has been histologically confirmed by a pathologist and (ii) associated with severe morbidity or functional limitations and not amenable to improvement with surgery determined consensually by qualified personnel (eg, 2 surgeons or a multi-disciplinary tumor board).

3. Measurable disease as defined by RECIST 1.1 (except that a minimal size of 2 cm is required), assessed from MRI scan by a central radiologist.
4. Stable prescription of analgesic regimen during the 2 weeks prior to enrollment.
5. Women of childbearing potential must have a negative serum pregnancy test within the 14-day period prior to enrollment (Where demanded by local regulations, this test may be required within 72 hours of enrollment).
6. Females of reproductive potential should be advised to use an effective, non-hormonal method of contraception during treatment with pexidartinib and for 1 month after the last dose. Males with female partners of reproductive potential should be advised to use an effective method of contraception during treatment with pexidartinib and for 1 month after the last dose. Female partners of male patients should concurrently use effective contraceptive methods (hormonal or non-hormonal). Women of nonchildbearing potential may be included if they are either surgically sterile or have been postmenopausal for ≥ 1 year. Women who have documentation of at least 12 months of spontaneous amenorrhea and have a follicle-stimulating hormone level > 40 mIU/mL will be considered postmenopausal.
7. Adequate hematologic, hepatic, and renal function, defined by:
    - Absolute neutrophil count $\geq 1.5 \times 10^9$/L
    - Hemoglobin > 10 g/dL
    - Platelet count $\geq 100 \times 10^9$/L
    - Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) $\leq 1.0 \times$ upper limit of normal (ULN)
    - Total bilirubin and direct bilirubin $\leq 1.0 \times$ ULN
    - Alkaline phosphatase $\leq 1.0 \times$ ULN
    - Creatinine clearance (CLcr) > 15 mL/min

8. Willingness and ability to complete the PROMIS Physical Function Scale.
9. Willingness and ability to use a diary.
10. Willingness and ability to provide written informed consent prior to any study-related procedures and to comply with all study requirements.

Exclusion Criteria:

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

1. Investigational drug/device use within 28 days of enrolment.
2. Previous use of pexidartinib or any biologic treatment targeting colony stimulating factor 1 (CSF-1) or the CSF-1 receptor; previous use of oral tyrosine kinase inhibitors are allowed (eg, imatinib or nilotinib).
3. Active cancer except for tumor for which a subject is enrolled in the study, (either concurrent or within the last year of starting study drug) that requires therapy (eg, surgical, chemotherapy, or radiation therapy), with the exception of adequately treated basal or squamous cell carcinoma of the skin, melanoma in-situ, carcinoma in-situ of the cervix or breast, or prostate carcinoma with a prostate-specific antigen value < 0.2 ng/mL.
4. Known metastatic TGCT.
5. Active or chronic infection with hepatitis C or known positive hepatitis B surface antigen, or known active or chronic infection with human immunodeficiency virus.
6. Active liver or biliary tract disease
7. Known active tuberculosis.
8. Significant concomitant arthropathy in the affected joint, serious illness, uncontrolled infection, or a medical or psychiatric history that, in the Investigator's opinion, would likely interfere with a subject's study participation or the interpretation of his or her results.

	9. Use of strong Cytochrome P450 (CYP) 3A inducers, including St John's wort, proton pump inhibitors (PPIs), and other products known to cause hepatotoxicity. 10. Women who are breastfeeding. 11. A screening Fridericia corrected QT interval (QTcF) ≥ 450 ms (men) or ≥ 470 ms (women). 12. MRI contraindications. 13. History of hypersensitivity to any excipients in the investigational product. 14. Inability to swallow capsules.
Dosage Form, Dose and Route of Administration:	The study drug, pexidartinib will be administered orally daily in capsule form. Each capsule contains 200 mg of pexidartinib (J-3397-AF in hypromellose capsules). Subjects will take 400 mg twice daily for a total daily dose of 800 mg (2 capsules in the morning and 2 capsules in the evening). The study drug must be taken on an empty stomach (no food for 1 hour before and 2 hours after dosing) at approximately the same time of the day with about 12-hour interval. Pexidartinib will be administered continuously with 28-day treatment cycle until criteria for discontinuation are reached.
Dose Modification Guidelines:	Reduction or interruption of dosing can be implemented at any time to manage intolerable or clinically significant toxicity as defined in the protocol. Permanently discontinue pexidartinib in subjects who are unable to tolerate 200 mg orally twice daily (400 mg/day pexidartinib).
Study Endpoints:	<u>Primary Endpoint</u>: The proportion of subjects who achieve a complete response (CR) or partial response (PR) of pexidartinib based on RECIST 1.1 at Week 25 by centrally reviewed MRI scan <u>Secondary Endpoints</u>: • Proportion of subjects who achieve a CR or PR of pexidartinib based on TVS at Week 25 by centrally reviewed MRI scan

- Mean change from baseline in range of motion of the affected joint, relative to a reference standard for the same joint, at the Week 25
- Mean change from baseline score in the PROMIS Physical Function Scale at the Week 25
- Best overall response (CR or PR) of pexidartinib based on RECIST 1.1 and TVS by centrally reviewed MRI scan
- Duration of response (CR or PR) of pexidartinib based on RECIST 1.1 and TVS by centrally reviewed MRI scan
- Safety endpoints included the following, but not limited to: Treatment-emergent adverse events (TEAEs), laboratory tests, vital sign, and Electrocardiograms (ECGs)
- Pharmacokinetics (PK) of pexidartinib and its primary metabolite, ZAAD-1006a

Exploratory Endpoints:

- Proportion of subjects who achieve a CR or PR of pexidartinib based on RECIST 1.1 at Week 25 by locally reviewed MRI scan
- Proportion of subjects who achieve a CR or PR of pexidartinib based on modified RECIST 1.1-SSD at Week 25 by centrally reviewed MRI scan
- Mean change from baseline score in the EQ-5D-5L at the Week 25
- Best overall response (CR or PR) of pexidartinib based on RECIST 1.1 by locally reviewed MRI scan
- Duration of response (CR or PR) of pexidartinib based on RECIST 1.1 by locally reviewed MRI scan
- Duration of response (CR or PR) of pexidartinib based on modified RECIST 1.1-SSD by centrally reviewed MRI scan
- Photographic documentation of tumor size change

	• Results of the Surgical Assessment Questionnaire • PDy of plasma CSF-1 activity • Long term subject status after the end-of-study or early termination visit
Planned Sample Size:	Approximately 35 subjects across multiple sites in China and Taiwan.
Statistical Analyses:	The primary endpoint is the proportion of subjects who achieve a CR or PR of pexidartinib based on RECIST 1.1 at Week 25 by centrally read MRI scan. The estimate of the proportion and 95% exact confidence interval (CI) will be provided. The proportions and mean changes of the secondary endpoints will be summarized. Duration of responses of the secondary efficacy endpoints will be summarized descriptively using the Kaplan-Meier method. Safety variables, including TEAEs, laboratory tests, vital signs, and ECGs, will be summarized.

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GLOBAL AMENDMENT, PROTOCOL VERSION 4.0

Amendment Rationale:

The main purpose of this amendment is to remove Pharmacogenomics (PGx) test in exploratory objectives in PL3397-A-A303 study due to HGRAC rejection.

Changes to the Protocol:

Please refer to the comparison document for protocol version 3.0 (dated 25 Feb 2020) vs. protocol version 4.0 (dated 29 Jan 2021) for actual changes in-text. The summary of changes below is a top-line summary of major changes in the PL3397-A-A303 clinical study protocol (Version 4.0) by section.

DESCRIPTION OF EACH HIGH-LEVEL CHANGE	
1	**Updated INVESTIGATOR AGREEMENT.** Sponsor Approval name was updated.
2	**Updated study objectives.** PGx was removed.
3	**Updated exploratory endpoints.** PGx was removed.
4	**Update LIST OF ABBREVIATIONS** "HGRAC" was added.
5	**Updated 6.3.1. Cycle 1, Day 1 (C1D1; Week 1)** "Blood sampling for PGx analysis" was removed.
6	**Update 7.1.1. Tumor Imaging** "Standard operation of the sites" was added.
7	**Updated 7.3. Exploratory Efficacy Endpoint** PGx was removed.
8	**Updated 8. PHARMACOKINETIC/PHARMACODYNAMIC/ PHARMACOGENOMIC ASSESSMENTS** "PGx endpoints" was removed.
9	**Updated Schedule of Assessment** PGx was removed.

LIST OF ABBREVIATIONS

Abbreviation or Term	Definition/Explanation
AE	Adverse event
ALT	Alanine aminotransferase
AMA	Anti-mitochondrial antibody
AST	Aspartate aminotransferase
AUC6h	Area under the plasma-concentration-time curve from time 0 h to 6 h
AUCinf	Area under the plasma-concentration-time curve from time zero to infinity
BID	Twice daily
BP	Blood pressure
C1D1	Cycle 1 Day 1
CI	Confidence Interval
CLcr	Creatinine clearance
Cmax	Peak drug concentration
CR	Complete response
CRO	Contract Research Organization
CSF-1	Colony stimulating factor 1
CSF1R	Colony-stimulating factor 1 receptor
CTCAE	Common Terminology Criteria for Adverse Events
CYP	Cytochrome P450
DS	Daiichi Sankyo
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic data capture
EIU	Exposure in utero
EQ-5D-5L	EuroQol five-dimensional descriptive system
FAS	Full analysis set
FDA	Food and Drug Administration
FLT3	FMS-like tyrosine kinase 3
FSH	Follicle-stimulating hormone
GCP	Good Clinical Practice
GCT-TS	Giant cell tumor of the tendon sheath

Abbreviation or Term	Definition/Explanation
GGT	Gamma-glutamyl transpeptidase
H_2	histamine 2
HEAC	External hepatic adjudication committee
HGRAC	Human Genetics Resources Administration of China
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IEC	Independent ethics committee
INR	International normalized ratio
IRB	Institutional review board
ITD	Internal tandem duplication
KIT	KIT proto-oncogene receptor tyrosine kinase
LH	Luteinizing hormone
MedDRA	Medical Dictionary for Drug Regulatory Activities
MRI	Magnetic resonance imaging
MTD	Maximum tolerated dose
NCI	National Cancer Institute
NE	Not evaluable
ORR	Overall response rate
OTC	Over-the-counter
PD	Progressive disease
PDy	Pharmacodynamic(s)
PK	Pharmacokinetic
PopPK	Population pharmacokinetic
PPI	Proton pump inhibitor
PR	Partial response
PRO	Patient-reported outcomes
PROMIS	Patient-reported Outcomes Measurement Information System
PT	Preferred term
PVNS	Pigmented villonodular synovitis
QTc	Corrected QT interval

Abbreviation or Term	Definition/Explanation
QTcF	QT interval using Fridericia's formula
RECIST	Response Evaluation Criteria in Solid Tumors
RP2D	Recommended Phase 2 Dose
SAE	Serious adverse event
SAP	Statistical analysis plan
SAVER	Serious Adverse Event Report
SCF	Stem cell factor
SD	Stable disease
SMC	Safety monitoring committee
SOC	System organ class
SSD	Sum of the short-axis dimension
SUSAR	Suspected unexpected serious adverse reaction
TEAE	Treatment-emergent adverse event
TGCT	Tenosynovial giant cell tumor
Tmax	Time of maximum observed concentration
TVS	Tumor Volume Score
UGT	Uridine 5'-diphospho-glucuronosyltransferase
ULN	Upper limit of normal
US	United States
WORMS	Whole organ MRI score

1. INTRODUCTION

A comprehensive review of pexidartinib (PLX3397) is contained in the Investigator's Brochure (IB). Investigators should review the latest IB prior to initiating this study. A brief review of pexidartinib is provided here.

1.1. Scientific Background

1.1.1. Tenosynovial giant cell tumor (TGCT)

Tenosynovial giant cell tumor (TGCT) is a rare, nonmalignant neoplasm of the synovium, bursae, or tendon sheaths, affecting generally young adults (< 40 years of age) of both sexes.[1] Symptoms initially may be minimal due to the slowly progressive nature of the disease. However, as the tumor mass grows and gradually expands within the intra- and extra-articular space, symptoms such as pain, stiffness, swelling, and reduced range of motion of the affected joint can become severe and result in debilitating functional limitations. The diagnosis of TGCT is based on pathologic evaluation; however, features highly suggestive of the disease may be found on radiologic imaging (ie, magnetic resonance imaging [MRI]).

TGCT manifests as localized or diffuse disease. The localized type (known as giant cell tumor of the tendon sheath [GCT-TS]) constitutes 80% to 90% of TGCT cases and is usually a benign neoplasm that most commonly occurs in the digits.[1,2] Localized TGCT can usually be treated effectively with surgery. The diffuse type (known as pigmented villonodular synovitis [PVNS]) constitutes 10% to 20% of cases and is a locally aggressive, nonmalignant neoplasm composed of synovial-like mononuclear cells, multinucleate giant cells, foam cells, siderophages, and inflammatory cells that may be intra- or extra-articular. Diffuse TGCT most commonly occurs in large joints, particularly the knee, ankle, and hip.[1,2] In the United States (US), the annual incidence of new cases is estimated to be ~15,000 for localized TGCT and ~1500 for diffuse TGCT.[1,3,4] A more recent survey in Denmark provides an incidence of 4.4 per million for localized TGCT and 1.2 per million for diffuse TGCT,[2] whereas a study in the Netherlands reports incidence rates (per million patient-years) of 34 for localized TGCT in the digits, 11 for localized disease in other extremities, and 5 for diffuse TGCT.[5]

TGCT predominantly consist of mononuclear and multinucleated giant cells. Expansion of the tumor mass appears to be driven by the presence of abundant colony stimulating factor 1 (CSF-1) expressed by a subset of neoplastic cells within the tumor and is often associated with genetic translocations, eg, linking the collagen 6A3 gene on chromosomal locus 2q35 with the CSF-1 gene on chromosomal locus 1p13.[6] The majority of cells in the tumor mass are non-neoplastic inflammatory cells that do not express CSF-1 but are attracted to the tumor site because of their expression of colony-stimulating factor 1 receptor (CSF1R).

The current standard of care for TGCT is surgical resection of the tumor as completely as possible to: (1) reduce pain, stiffness, and joint destruction caused by the disease process; (2) improve function; and (3) minimize the risk of recurrence. However, diffuse disease can be challenging to manage surgically. Patient outcome following surgery depends on multiple factors, including the location and extent of the disease. The overall recurrence rate for patients with focal disease is low, ranging from 0% to 6%[1]; however, in patients with diffuse forms of the disease, recurrence is considerably more common, and is estimated to be in the range of 40%.[7] Diffuse disease carries a risk of multiple recurrences, and affected patients often have more

extensive involvement and a poorer likelihood of success with surgery. Surgical resection may involve removal of major tendons or neurovascular structures, leading to significant postsurgical morbidity. Limb amputation may be required in severe, recurrent cases.[1]

No systemic antitumor agents had been approved for this indication.[8] Anti-inflammatory and analgesic medications, including opioids, had been commonly used as supportive therapy. In light of the severe morbidity that a patient can experience with this disease, a systemic therapy that provides a meaningful clinical benefit is highly needed.

1.1.2. Pexidartinib (PLX3397)

Pexidartinib is a small molecule tyrosine kinase inhibitor that targets CSF1R, KIT proto-oncogene receptor tyrosine kinase (KIT), and feline McDonough FMS-like tyrosine kinase 3 (FLT3) harboring an internal tandem duplication (ITD) mutation. Pexidartinib inhibited the proliferation of cell lines that depend on CSF1R at concentrations below 1 μmol/L. Ligand-induced autophosphorylation of CSF1R is also inhibited by pexidartinib. Pexidartinib has been approved in the US for the treatment of TGCT associated with severe morbidity or functional limitations and amenable to improvement with surgery.

1.2. Nonclinical Studies

The effects of pexidartinib on multiple aspects of tumorigenesis have been characterized with in vitro and in vivo assays. The proliferation of cell lines that depend on CSF-1, stem cell factor (SCF), or endogenous FLT3-ITD mutation is inhibited at half maximal inhibitory concentration values below 1 μmol/L. Furthermore, CSF-1 induced autophosphorylation of CSF1R and SCF-induced autophosphorylation of KIT are potently inhibited by pexidartinib. Finally, the receptor activator of NF-kappa B ligand-dependent 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 cell proliferation.

While pharmacologic effects due to the inhibition of CSF1R and KIT are expected, the relative selectivity of pexidartinib against other kinases suggests that off-target effects against other kinases should be reduced.

Additional detailed information regarding the nonclinical pharmacology and toxicology of pexidartinib can be found in the IB.[9]

1.3. Clinical Experience

As of 31 Jul 2018, pexidartinib has been evaluated in 28 company-sponsored clinical studies in healthy subjects and in patient populations (cancer and TGCT). Pexidartinib were administered to 645 subjects with cancer or TGCT in company-sponsored clinical studies.

1.3.1. Patients with TGCT Treated in the Phase 1 Study PLX108-01

This study is evaluating subjects with advanced, incurable, solid tumors in which the target kinases are linked to disease pathophysiology. This study is being conducted in 2 parts: an initial dose-escalation part to identify a recommended Phase 2 dose (RP2D), and an extension part to

obtain preliminary efficacy data in subjects with selected tumor types. The dose escalation part of the study has been completed and 1000 mg/day, administered as a twice daily (BID) regimen, was selected as the maximum tolerated dose (MTD) and RP2D for further evaluation in the extension cohorts.

In the extension phase of the study, as of the 31 March 2017 data cut-off, treatment with pexidartinib (1000 mg/day) in the TGCT cohort (2 of 37 subjects) showed a Best Overall Response of 62.2% (95% confidence interval [CI]: 42.1%, 75.2%) by investigator assessment according to Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1). Similar efficacy results were observed based upon central MRI review. Many of the responding subjects have been continuing treatment for more than 2 years.

As of the 31 January 2018 data cut-off, all 39 (100%) subjects experienced at least 1 treatment-related treatment-emergent adverse event (TEAE), and 35.9% of subjects experienced a Grade ≥ 3 treatment-related TEAE. The most frequently occurring treatment-related TEAEs were fatigue (74.4%), hair color changes (71.8%), and nausea (56.4%). The most common Grade ≥ 3 treatment-related TEAEs were hypophosphatemia (10.3%); alanine aminotransferase (ALT) increased (10.3%); aspartate aminotransferase (AST) increased (7.7%); hyponatremia (5.1%); and fatigue, diarrhea, anemia, neutropenia, arthritis, and transaminases increased (1 subject [2.6%] each). As of the 03 Mar 2017 data cut-off, in the TGCT cohort of Study PLX108-01, 4 (10.3%) subjects treated with pexidartinib experienced serious TEAEs. The serious TEAEs reported were cholecystitis, renal cell carcinoma, hyponatremia, neck pain, and renal failure acute. No new serious TEAEs or deaths due to adverse events (AEs) were reported between 03 Mar 2017 and 31 Jan 2018.

Further details on the clinical experience with pexidartinib can be found in the IB.[9]

1.3.2. Patients with TGCT Treated in the Phase 3 Study PLX108-10

This study (PLX108-10) is a 2-part, multicenter, Phase 3 study in subjects with TGCT, for whom surgical resection would be associated with potentially worsening functional limitation or severe morbidity (locally advanced disease). In Part 1 (double blind phase), eligible candidates were centrally randomized in a 1:1 ratio to receive either pexidartinib or placebo for 24 weeks (1000 mg/day [400 mg in the morning and 600 mg in the evening] or placebo for the first 2 weeks and 800 mg/day [400 mg BID] or placebo for 22 weeks). Those subjects who complete Part 1 (ie, 24 weeks of dosing) were eligible to advance to Part 2, a long-term treatment phase where all subjects received open-label pexidartinib at a maximum starting dose of 800 mg/day.

The primary objective of this study is to compare the response rate of pexidartinib with that of placebo at Week 25. The secondary efficacy objectives are to evaluate 1) range of motion at Week 25, 2) response based on TVS at Week 25, 3) patient-reported outcomes (PRO) at Week 25, and 4) duration of response.

PLX108-10 study demonstrated a statistically significant improvement ($p < 0.0001$) in overall response rate (ORR) at Week 25 in the 61 patients randomized to pexidartinib (37.7% [95% CI: 26.6%, 50.3%]) compared with placebo (0% [95% CI: 0, 6.1%]).

The rates of the most frequently occurring TEAEs at the 31 Jan 2018 data cut-off per subject receiving pexidartinib compared with placebo were hair color changes (74.7% vs 3.4%), AST increased (35.2% vs no subjects), ALT increased (28.6% vs 1.7%), dysgeusia (25.3% vs 1.7%),

pruritus (22.0% vs 3.4%), rash (20.9% vs 3.4%), periorbital edema (18.7% vs 1.7%), vomiting (15.4% vs 5.1%), face edema (15.4% vs 1.7%), edema peripheral (14.3% vs 3.4%), rash maculo-papular (12.1% vs 1.7%), alkaline phosphatase (ALP) increased (11.0% vs no subjects), and lactate dehydrogenase increased (11.0% vs no subjects). For subjects who received pexidartinib in Part 1 and/or Part 2, the proportion of subjects reporting TEAEs of Common Terminology Criteria for Adverse Events (CTCAE) Grade ≥ 3 considered treatment-related (38.5%) was similar to that reported for subjects receiving pexidartinib in Part 1 (37.7%).

1.3.3. Patients with Solid Tumor Treated in the Phase 1 Study PL3397-A-A103

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

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

The dose-escalation part of the study showed that daily oral dosing of pexidartinib in 28-day cycles was safe and tolerated up to 1000 mg/day in Asian subjects with advanced solid tumors. No dose limiting factor was observed and the MTD was determined 1000 mg/day. The RP2D of pexidartinib was determined as 1000 mg/day based on MTD. Pexidartinib exposure parameters increased with increasing dose. Following multiple-dose administration of pexidartinib, plasma concentrations of CSF-1 and adiponectin increased dose-dependently. Antitumor activity was observed in both cohorts. In Asian subjects with advanced solid tumors, pexidartinib was well-tolerated, with a safety profile consistent with that previously reported from the first human study in US.

1.4. Study Rationale

The current study will be a multicenter, single arm Phase 3 study in Asian subjects with symptomatic TGCT associated with severe morbidity or functional limitations and not amenable to improvement with surgery. The subject population to be studied in this study will be the almost same as in the PLX108-10 study.

The primary endpoint in this study is the proportion of subjects who achieve a complete response (CR) or partial response (PR) based on centrally read MRI responder criteria as defined by RECIST 1.1 at Week 25, the same as that defined in the PLX108-10 study. The MRI will be assessed at every 12 weeks. A subject will be considered to have a response if the tumor meets the criteria for response and has a documented nonprogression at Week 25. To minimize bias and reduce variability from this single arm study, centralized review of the MRI will be performed by the blinded readers. The Imaging Charter for this study describes the image acquisition standards and methodology to be used as well as the standards for image interpretation.

The secondary endpoints are: (i) response based on tumor volume score (TVS) at Week 25; (ii) range of motion at Week 25; (iii) Patient-reported Outcomes Measurement Information System (PROMIS) Physical Function Scale at Week 25; (iv) best overall response; (v) duration of response; (vi) safety; and (vii) PK.

The endpoint of TVS by the use of central MRI readers will be reinforced for the primary imaging endpoint of RECIST 1.1 assessment. The endpoint of PROMIS assessment or improvement of range of motion will reinforce the explanation of clinical benefit from primary imaging endpoint.

1.5. Risks and Benefits for Study Subjects

Pexidartinib has been approved in the US for the treatment of TGCT associated with severe morbidity or functional limitations and amenable to improvement with surgery.

Safety data from nonclinical studies, clinical studies, and non-interventional studies have been reviewed. Liver toxicity is an important identified risk, and both embryo-fetal toxicity and fertility toxicity are considered an important potential risk with pexidartinib. Hepatotoxicity may be fatal, and liver transplantation may be required. The benefit/risk of pexidartinib specific for each study population should be assessed in study protocols. Risk minimization measures, such as frequent monitoring during the first 8 weeks of pexidartinib treatment, related to managing these risks should be included in all study protocols.

2. STUDY OBJECTIVES AND HYPOTHESIS

2.1. Study Objectives

The purpose of this study is to evaluate the efficacy and safety of pexidartinib treatment in the Asian subjects with symptomatic TGCT associated with severe morbidity or functional limitations and not amenable to improvement with surgery. The primary endpoint of the study is the proportion of subjects who achieve a CR or PR of pexidartinib based on RECIST 1.1 at Week 25 by centrally reviewed MRI scan.

2.1.1. Primary Objective

To evaluate the efficacy in the Asian patients with TGCT by determining the ORR of pexidartinib based on RECIST 1.1 at Week 25 by centrally reviewed MRI scan.

2.1.2. Secondary Objectives

To evaluate:

- Response of pexidartinib based on TVS at Week 25 by centrally reviewed MRI scan
- Range of motion at Week 25
- PROMIS Physical Function Scale at Week 25
- Best overall response of pexidartinib based on RECIST 1.1 by centrally reviewed MRI scan
- Best overall response of pexidartinib based on TVS by centrally reviewed MRI scan
- Duration of response of pexidartinib based on RECIST 1.1 by centrally reviewed MRI scan
- Duration of response of pexidartinib based on TVS by centrally reviewed MRI scan
- Safety
- PK

2.1.3. Exploratory Objectives

To evaluate:

- ORR of pexidartinib based on RECIST 1.1 at Week 25 by locally reviewed MRI scan
- ORR of pexidartinib based on modified RECIST 1.1-sum of the short-axis dimension (SSD) at Week 25 by centrally reviewed MRI scan
- EuroQol five-dimensional descriptive system (EQ-5D-5L)
- Best overall response of pexidartinib based on RECIST 1.1 by locally reviewed MRI scan
- Duration of response of pexidartinib based on RECIST 1.1 by locally reviewed MRI scan

- Duration of response of pexidartinib based on modified RECIST 1.1-SSD by centrally reviewed MRI scan
- Photographic documentation of tumor size change
- Results of the Surgical Assessment Questionnaire
- PDy
- Long term follow-up of the subject status after the end-of-study or early termination visit

2.2. Study Hypothesis

Pexidartinib is tolerable and efficacious and shows an acceptable safety profile when administered to subjects with symptomatic TGCT associated with severe morbidity or functional limitations and not amenable to improvement with surgery.

3. STUDY DESIGN

3.1. Overall Plan

This will be a multicenter, single arm study of pexidartinib orally administrated in adult subjects with symptomatic TGCT associated with severe morbidity or functional limitations and not amenable to improvement with surgery.

Study drug will be administered twice a day, every day. Subjects will take 400 mg twice daily for a total daily dose of 800 mg (2 capsules in the morning and 2 capsules in the evening). The study drug must be taken on an empty stomach at approximately the same time of the day with about 12-hour interval. The pexidartinib starting dose and treatment regimen in this study are based on the rationale of PLX108-10 study and the result of the Study PL3397-A-103.

The primary endpoint in this study is the proportion of subjects who achieve a CR or PR at the Week 25 based on criteria as defined by RECIST 1.1 by centrally reviewed MRI scan, the same as defined in the PLX108-10 study. The MRI will be assessed at every 3 months. A subject will be considered to have a response, if the tumor meets the criteria for response and has a documented nonprogression at Week 25. To minimize bias and reduce variability from this single-arm study, centralized review of the MRI image will be performed by blinded readers. The Imaging Charter for this study describes the image acquisition standards and methodology to be used as well as the standards for image interpretation.

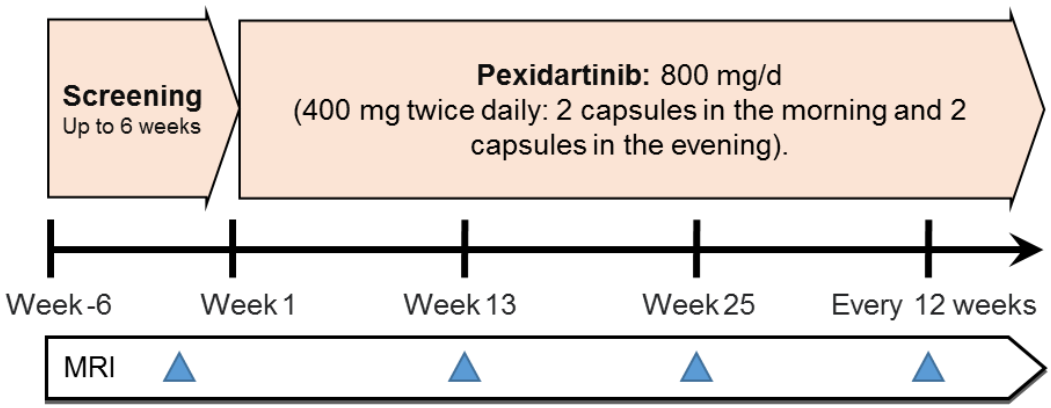
It is considered that tumor shrinkage is essential to improve symptoms for advanced TGCT subjects. The improvement of symptom will be evaluated with secondary endpoints. The endpoint of TVS by the use of central MRI readers will be reinforced for the primary imaging endpoint of RECIST 1.1 assessment. The endpoint of range of motion or PROMIS will reinforce the explanation of clinical benefit from primary imaging endpoint.

The data of PLX108-01 preliminary results suggests that the use of pexidartinib offers high tumor response rate to subjects with this diagnosis who would not be adequately treated with surgery, the existing only standard of care. The use of placebo will be an expected ethical limitation to enroll subject with symptomatic and surgical resection associated with potentially worsening functional limitation or severe morbidity under the circumstances of rare disease.

In addition, it is considered that the primary endpoint will assess the durable response of 6 months by RECIST 1.1 criteria that the primary endpoint for tumor shrinkage in between pre- and post-treatment with centralized review of all MRI scans will be conducted and that the study will be conducted without the use of placebo. Moreover, the endpoint of TVS by use of central MRI readers will be reinforced for the primary imaging endpoint of RECIST 1.1 assessments. In consideration of the below illustrated aspects, a single arm study without placebo control group has been planned.

After completion of the end-of-study or early termination visit, subject status will be collected every 6 months as a long term follow-up at least 2 years.

Figure 3.1: Study Schema



MRI: magnetic resonance imaging.

3.1.1. Duration of Subject Participation

Each subject will spend a maximum of 6 weeks in screening. All subjects will continue in the study until disease progression, unacceptable toxicity, or any of the other termination criteria. (See Section 14.8)

Primary analysis will be performed after the last subject completes the Week 25 assessments.

The duration after the Week 25 assessments will vary among subjects, as this portion of the study will continue until all subjects have either completed the study drug or withdrawn from the study.

3.1.2. Study Endpoints

3.1.2.1. Primary Endpoint

The primary endpoint is the proportion of subjects who achieve a CR or PR of pexidartinib based on RECIST 1.1 at Week 25 by centrally reviewed MRI scan.

3.1.2.2. Secondary Endpoints

The following evaluations comprise the secondary endpoints:

- Proportion of subjects who achieve a CR or PR of pexidartinib based on TVS at Week 25 by centrally reviewed MRI scan
- Mean change from baseline in range of motion of the affected joint, relative to a reference standard for the same joint, at the Week 25
- Mean change from baseline score in the PROMIS Physical Function Scale at the Week 25
- Best overall response (CR or PR) of pexidartinib based on RECIST 1.1 by centrally reviewed MRI scan

- Best overall response (CR or PR) of pexidartinib based on TVS by centrally reviewed MRI scan
- Duration of response (CR or PR) of pexidartinib based on RECIST 1.1 by centrally reviewed MRI scan
- Duration of response (CR or PR) of pexidartinib based on TVS by centrally reviewed MRI scan
- Safety endpoints included the following, but not limited to: TEAEs, laboratory tests, vital sign, and Electrocardiogram (ECG)s
- PK of pexidartinib and its primary metabolite, ZAAD-1006a

3.1.2.3. Exploratory Endpoints

Exploratory endpoints to be analyzed at appropriate time points include:

- Proportion of subjects who achieve a CR or PR of pexidartinib based on RECIST 1.1 at Week 25 by locally reviewed MRI scan
- Proportion of subjects who achieve a CR or PR of pexidartinib based on modified RECIST 1.1-SSD at Week 25 by centrally reviewed MRI scan
- Mean change from baseline score in the EQ-5D-5L at the Week 25
- Best overall response (CR or PR) of pexidartinib based on RECIST 1.1 by locally reviewed MRI scan
- Duration of response (CR or PR) of pexidartinib based on RECIST 1.1 by locally reviewed MRI scan
- Duration of response (CR or PR) of pexidartinib based on modified RECIST 1.1-SSD by centrally reviewed MRI scan
- Photographic documentation of tumor size change
- Results of the Surgical Assessment Questionnaire
- PDy of plasma CSF-1 activity
- Long term subject status after the end-of study or early termination visit

In addition to standard RECIST 1.1, which is based on the longest unidimensional measurement, an exploratory endpoint will be the response based on centrally read MRI and the SSD of the tumor (modified RECIST 1.1-SSD).

Short-axis measurements will be made perpendicular to a reproducible adjacent landmark such as the femoral bone or a tendon, where the tumor dimension appears greatest and yet confidently measurable. Measurement of this site will be repeated on the other visits. The tumor response status on this endpoint within 24 weeks of treatment will be determined in a way similar to that for the primary endpoint.

4. STUDY POPULATION

Subjects 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

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

1. Age ≥ 18 years (Age ≥ 20 years in Taiwan).
2. A diagnosis of TGCT (i) that has been histologically confirmed by a pathologist and (ii) associated with severe morbidity or functional limitations and not amenable to improvement with surgery determined consensually by qualified personnel (eg, 2 surgeons or a multi-disciplinary tumor board).
3. Measurable disease as defined by RECIST 1.1 (except that a minimal size of 2 cm is required), assessed from MRI scan by a central radiologist.
4. Stable prescription of analgesic regimen during the 2 weeks prior to enrollment.
5. Women of childbearing potential must have a negative serum pregnancy test within the14-day period prior to enrollment (Where demanded by local regulations, this test may be required within 72 hours of enrollment).
6. Females of reproductive potential should be advised to use an effective, non-hormonal method of contraception during treatment with pexidartinib and for 1 month after the last dose. Males with female partners of reproductive potential should be advised to use an effective method of contraception during treatment with pexidartinib and for 1 month after the last dose. Female partners of male patients should concurrently use effective contraceptive methods (hormonal or non-hormonal). Women of nonchildbearing potential may be included if they are either surgically sterile or have been postmenopausal for ≥ 1 year. Women who have documentation of at least 12 months of spontaneous amenorrhea and have a follicle-stimulating hormone level > 40 mIU/mL will be considered postmenopausal.
7. 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 ≤ 1.0 ×upper limit of normal (ULN)
   - Total bilirubin and direct bilirubin ≤ 1.0 × ULN
   - Alkaline phosphatase ≤ 1.0 × ULN
   - Creatinine clearance (CLcr) > 15 mL/min
8. Willingness and ability to complete the PROMIS Physical Function Scale.
9. Willingness and ability to use a diary.

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

4.2. Exclusion Criteria

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

1. Investigational drug/device use within 28 days of enrollment.
2. Previous use of pexidartinib or any biologic treatment targeting CSF-1 or the CSF1R; previous use of oral tyrosine kinase inhibitors are allowed, (eg, imatinib or nilotinib).
3. Active cancer except for tumor for which a subject is enrolled in the study, (either concurrent or within the last year of starting study drug) that requires therapy (eg, surgical, chemotherapy, or radiation therapy), with the exception of adequately treated basal or squamous cell carcinoma of the skin, melanoma in-situ, carcinoma in-situ of the cervix or breast, or prostate carcinoma with a prostate-specific antigen value < 0.2 ng/mL.
4. Known metastatic TGCT.
5. Active or chronic infection with hepatitis C or known positive hepatitis B surface antigen, or known active or chronic infection with human immunodeficiency virus.
6. Active liver or biliary tract disease.
7. Known active tuberculosis.
8. Significant concomitant arthropathy in the affected joint, serious illness, uncontrolled infection, or a medical or psychiatric history that, in the Investigator's opinion, would likely interfere with a subject's study participation or the interpretation of his or her results.
9. Use of strong cytochrome P450 (CYP) 3A inducers, including St John's wort, proton pump inhibitors (PPIs), and other products known to cause hepatotoxicity.
10. Women who are breastfeeding.
11. A screening Fridericia corrected QT interval (QTcF) ≥ 450 ms (men) or ≥ 470 ms (women).
12. MRI contraindications.
13. History of hypersensitivity to any excipients in the investigational product.
14. Inability to swallow capsules.

4.3. Subject Replacement

Subjects withdrawn from the study will not be replaced.

4.4. Subject Re-screening Procedures

Rescreening is permitted for any candidate who failed to meet the eligibility criteria upon initial screening. If rescreened, the candidate will not be given a new subject identification number.

The initial screening information and the reason why the subject was not eligible for the initial evaluation will be recorded on the screening log. However, MRI, range of motion and surgical assessment may not need to be repeated, following consultation with Daiichi Sankyo (DS) Medical Monitor.

5. STUDY TREATMENT

5.1. Assigning Subjects to Treatments and Blinding

5.1.1. Treatment Group

This is a single arm study. Eligible subjects will receive 400 mg twice daily for a total daily dose of 800 mg (2 capsules in the morning and 2 capsules in the evening).

Treatment duration of pexidartinib is presented in Section 3.1.1.

5.1.2. Method of Treatment Allocation

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

5.1.3. Blinding

This study is open-label and no blinding will be performed for the study drug. However, all MRI images (scans) will be assessed by central readers blinded to study subject information according to procedures outlined in a separate MRI Imaging Charter.

5.1.4. Emergency Unblinding Procedure

Not applicable.

5.2. Study Drug

5.2.1. Description

Pexidartinib is a hydrochloride salt with a white to off-white crystalline solid appearance. Pexidartinib supplied as a hypromellose 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.

5.2.2. Labeling and Packaging

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

5.2.3. Preparation

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

5.2.4. Administration

Study drug will only be given to enrolled subjects under the supervision of the principal investigator or identified subinvestigator(s). The study drug for home administration during the study will be dispensed to the subject for the first time at the Cycle 1 Day 1 (C1D1) visit (within 3 days of enrollment). Capsules must be swallowed and not crushed, chewed, or dissolved in liquid. In this study, subjects will only receive pexidartinib capsules.

Study drug administration will begin at the C1D1 visit in the morning. At this visit, subjects will be instructed to take 400 mg BID for a total daily dose of 800 mg (2 capsules in the morning and 2 capsules in the evening) through the study. The study drug must be taken on an empty stomach at approximately the same time of the day with about 12-hour interval. Each dosing cycle will be of 28 days.

For the C1D15 visit (Week 3) and any visit when an ECG and PK will be performed, subjects must be told to NOT take their morning dose of study drug while coming for the study visit, which should be scheduled in the morning. The subject must be instructed to bring their bottle of study drug to the site and take their morning dose upon instruction by the study site. The time of dosing must be recorded. Subjects will then take their evening dose at home. If dose administered at the site is taken in the afternoon, then the subject must be instructed to skip their evening dose for that day.

For the C7D1 visit (Week 25), subjects must be told to NOT take the morning dose of study drug before their visit and bring all unused capsules to the site for accountability. Subjects who continue the study will be taking the same number of pexidartinib capsules per day as they will be taking at the end of 24 weeks treatment, ie, a maximum dose of 800 mg/day pexidartinib.

Between site visits, subjects 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 hours dosing window) must be skipped and NOT administered as a double dose at the next dosing time point. Subjects who vomit their dose must be instructed NOT to make up that dose.

Further details on study drug administration are present in the Study Pharmacy Manual.

5.2.5. Storage

The study drug (pexidartinib) must be stored up to 25°C (77°F) in a secure, limited access storage area. Excursion is permitted up to 30°C (86°F).

If storage conditions are not maintained per specified requirements, then DS or Contract Research Organization (CRO) must be contacted. Subjects are to be instructed to store the study drugs at room temperature out of the reach of children or other cohabitants.

5.2.6. Drug Accountability

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

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

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

At the end of the study, or as directed, all study drugs (including unused, partially used, or empty containers) will be returned to a designee as instructed by DS. Study drug will be returned only after the study monitor has completed a final inventory to verify the quantity to be returned. The return of study drug must be documented and the documentation must be included in the shipment. At the end of the study, a final study drug reconciliation statement must be completed by the Investigator or designee and provided to DS.

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

5.3. Control Treatment

Not applicable.

5.4. Dose Modification

Reducing or interrupting the dose for toxicity may take place at any time during the study according to the guidelines in Table 5.1 and Table 5.2. Dose modification guidelines for hematologic and hematologic 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 must be performed as scheduled, irrespective of the study drug delay, with the exception of PK assessments which must be deferred until treatment is resumed.

When an odd number of capsules are taken in a day, the larger number of capsules must be taken as the evening dose. For example, 600 mg/day = 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 must be the same (eg, 800 mg/day = 4 capsules [2 capsules in the morning and 2 capsules in the evening] or 400 mg/day = 2 capsules [1 capsule in the morning and 1 capsule in the evening]).

Dose reductions must be applied in increments of 200 mg/day (1 capsule), with a maximum total reduction of 400 mg/day (ie, a minimum dose of 400 mg/day). Subjects unable to tolerate 400 mg/day (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 DS's Medical Monitor or designee.

Table 5.1: Dose Modification

Dose reduction	Total daily dose	Administration of total daily dose
First	600 mg	200 mg in the morning and 400 mg in the evening
Second	400 mg	200 mg twice daily

Dose modification guidelines for treatment-emergent toxicities as well as guidelines for their management are presented in Table 5.2. These parameters are only a guide and are not intended to supersede the clinical judgment of the treating Investigator. All adjustments must be communicated to DS's Medical Monitor or designee. Additional liver evaluation is presented in Table 5.3. Rechallenge with a reduced dose of pexidartinib may result in a recurrence of increased serum transaminases, bilirubin, or ALP. Monitor liver tests weekly for the first month after rechallenge.

Table 5.2: Dose Modification Guidelines for Treatment-emergent Toxicities

Adverse Reaction	Severity	Pexidartinib Dosage Modifications
Increased ALT and/or AST	Greater than 3 to 5 times ULN	• Withhold and monitor liver tests weekly. • If AST and ALT are less than or equal to 3 times ULN within 4 weeks, resume at reduced dose. • If AST or ALT is not less than or equal to 3 times ULN in 4 weeks, permanently discontinue pexidartinib. • If AST or ALT is not less than or equal to 3 times ULN in 2 weeks, proceed to liver evaluation as outlined in Table 5.3
	Greater than 5 to 10 times ULN	• Withhold and monitor liver tests twice weekly. If AST and ALT are less than or equal to 3 times ULN within 4 weeks, resume at reduced dose. • If AST or ALT is not less than or equal to 3 times ULN in 4 weeks, permanently discontinue pexidartinib. • If AST or ALT is not less than or equal to 3 times ULN in 2 weeks, proceed to liver evaluation as outlined in Table 5.3
	Greater than 10 times ULN	• Permanently discontinue pexidartinib. • Monitor liver tests twice weekly until AST or ALT is less than or equal to 5 times ULN, then weekly until less than or equal to 3 times ULN. • Proceed to liver evaluation as outlined in Table 5.3

Increased ALP and Gamma-glutamyl transpeptidase (GGT)	ALP greater than 2 times ULN with GGT greater than 2 times ULN	• Permanently discontinue pexidartinib. • Monitor liver tests twice weekly until ALP is less than or equal to 5 times ULN, then weekly until less than or equal to 2 times ULN. • Proceed to liver evaluation as outlined in Table 5.3
Increased bilirubin	Total bilirubin greater than ULN to less than 2 times ULN or Direct bilirubin greater than ULN and less than 1.5 times ULN	• Withhold and monitor liver tests twice weekly. • If an alternate cause for increased bilirubin is confirmed and bilirubin is less than ULN within 4 weeks, resume at reduced dose. • If bilirubin is not less than ULN in 4 weeks, permanently discontinue pexidartinib. • If bilirubin is not less than ULN in 2 weeks, proceed to liver evaluation as outlined in Table 5.3
	Total bilirubin greater or equal to 2 times ULN or Direct bilirubin greater than 1.5 times ULN	• Permanently discontinue pexidartinib. • Monitor liver tests twice weekly until bilirubin is less than or equal to ULN. • Proceed to liver evaluation as outlined in Table 5.3
Adverse reactions or other laboratory abnormalities	Severe or intolerable	• Withhold until improvement or resolution. • Resume at a reduced dose upon improvement or resolution.

ALT = alanine aminotransferase; ALP = alkaline phosphatase; AST = aspartate aminotransferase; GGT = gamma-glutamyl transpeptidase; ULN = upper limit of normal

Table 5.3: Additional Liver Evaluation

Evaluation	Instruction
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.
Detail medical history and physical examination seeking new abnormalities.	Evaluate any abnormalities found.
Full serological evaluation for hepatitis A, B, C, D, and E (IgG and IgM). Check for autoimmune hepatitis with serological laboratory studies.	If viral hepatitis or autoimmune hepatitis suggested, have subject evaluated by hepatologist.

Perform liver ultrasound to evaluate liver and biliary tree.	Evaluate any abnormalities found.
Check history for exposure to chemical agents.	Remove chemical exposure and have subject seen by hepatologist.
Obtain hepatology consult if liver function continues to rise beyond 14 day.	Contact Medical Monitor.
Measure AMA.	Evaluate any abnormalities found.
Perform liver biopsy to evaluate the pathological change (if possible).	Evaluate any abnormalities found.
We request that cases be discussed with the Medical Monitor in instances where study drug is being held for liver function test abnormalities.	

OTC = over-the-counter; AMA = anti-mitochondrial antibody

5.5. Method of Assessing Treatment Compliance

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

Subjects 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, subjects will be assessed for compliance with study drug administration, ie, actual capsules taken/expected capsules taken. The subject must also return all bottles (used/unused) at each dispensing visit.

Further details can be found in each manual.

5.6. Prior and Concomitant Medications

During the study, if the use of any concomitant treatment becomes necessary (eg, for treatment of an AE), the treatment must be recorded on the 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 day of C1D1 will be recorded on the eCRF. Analgesic use and analgesic regimen will be recorded.

Subjects enrolled in studies with pexidartinib and are receiving concomitant warfarin must 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) must be obtained just prior to initiation of pexidartinib, within 1 to 2 weeks after initiation, and periodically thereafter. Dose adjustments of warfarin must be made as medically indicated.

Avoid the concomitant use of pexidartinib with other products known to cause hepatotoxicity.

5.6.1. CYP3A inducers

Avoid the concomitant use of strong CYP3A inducers, including St John's wort (see Section16.1 , a list of common CYP3A inhibitors and inducers).

5.6.2. CYP3A and UGT inhibitors

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

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

Planned Total Daily Dose	Modified Total Daily Dose	Administration of Modified Total Daily Dose
800 mg	400 mg	200 mg BID
600 mg	400 mg	200 mg BID
400 mg	200 mg	200 mg once daily

5.6.3. Hormonal Contraceptives

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

5.6.4. Acid-reducing Agents

Avoid the concomitant use of PPIs while taking pexidartinib. As an alternative to a PPI, administer pexidartinib 2 hours before or 2 hours after taking a locally-acting antacid, or if using a histamine 2 (H_2)-receptor antagonist, administer pexidartinib at least 2 hours before or 10 hours after taking an H_2-receptor antagonist.

5.7. Dosage Modification for Renal Impairment

The recommended dosage of pexidartinib for patients with mild to severe renal impairment (CLcr 15 to 89 mL/min estimated by Cockcroft-Gault using actual body weight) is 200 mg in the morning and 400 mg in the evening.

5.8. Subject Withdrawal/Discontinuation

5.8.1. Reasons for Withdrawal

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

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

- AE
- Disease progression
- Subject request
- Investigator decision
- Protocol violation
- Surgery
- Subject noncompliance
- Pregnancy
- Study termination by DS or institutional review board (IRB)/independent ethics committee (IEC)

During the study, if a subject experiences radiological progression documented by central read, the subject may either be withdrawn from the study or, if the subject is continuing to have clinical benefit, the Investigator may consult with DS's Medical Monitor or designee to allow the subject to remain in the study.

5.8.2. Withdrawal Procedures

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

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

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

When a subject discontinues or is permanently withdrawn from the study, the Investigator will notify DS and ensure that the procedures listed in the "post-treatment visit" column in the Schedule of Assessment (Table 16.3) are performed 28 ± 7 days after the subject's last dose of

study drug and prior to initiating any new TGCT therapy, including surgery, whichever occurs first.

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

The reason for study withdrawal will be recorded. If a subject discontinues study drug to undergo surgery, information about the type of surgery and its outcome must be collected.

5.9. Long Term Follow-up

After completion of the end-of-study or early termination visit, subject status will be collected by telephone contact every 6 months as a long term follow-up at least 2 years from each subject who consent.

6. STUDY PROCEDURES

Study procedures are listed by visit in the following subsections. Additional details are provided in the MRI Procedure Manual, or Laboratory Manual as applicable.

Each subject must sign and date an ICF before undergoing any study procedure including screening procedures unless the screening procedure is considered standard of care.

Screening procedures are to be performed within 42 days before the first dose of study drug, unless otherwise noted.

If a dose interruption is required, study assessments must be performed as scheduled, irrespective of the study drug delay, with the exception of PK assessments which should be deferred until treatment is resumed.

6.1. Screening

6.1.1. Screening (Day –42 to Day –1)

The following procedures must be performed within the 42-day period before C1D1, unless otherwise noted, and the results must be obtained and evaluated for eligibility prior to the C1D1 visit:

To be performed before any procedures:

- Informed consent

Before any invasive procedures carried out on the same day, the following parameters are to be recorded:

- Vital signs, including blood pressure (BP), pulse rate, and temperature
- 12-lead ECG

Other procedures to be performed:

- Medical history (including TGCT treatment history and smoking history)
- Demographics, including ethnicity and race
- Assessment of concomitant medications including analgesics
- PROMIS Physical Function Scale
- EQ-5D-5L
- Surgical Assessment Questionnaire
- Height and weight
- Physical examination
- Clinical laboratory tests: serum chemistry, hematology, liver function, hepatitis panel, hormone testing (as applicable) *, serum pregnancy testing (as applicable)**
- MRI of the affected joint within 56 days prior to C1D1
- Photographic documentation of tumor

- Range of motion assessment of the affected joint
- AE assessment
- Serum sample for anti-mitochondrial antibody (AMA)

  * Note: Women who are not using hormonal contraception must be tested for levels of follicle-stimulating hormone (FSH), luteinizing hormone (LH), progesterone, and estradiol. Hormone testing will not be required for women who have either had an oophorectomy or are postmenopausal. Men must be tested for levels of LH, FSH, and testosterone. Men whose testosterone level is below baseline at the last study visit must be followed until their level has stabilized or returned to baseline.

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

6.2. Enrollment

6.2.1. Cycle 1 (Enrollment)

To be performed after the subject is determined to meet all eligibility criteria:

- Subject enrollment (can be done up to 3 days prior to C1D1)

6.3. Treatment Period

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

Before any invasive procedures, the following parameters are to be recorded:

- PROMIS Physical Function Scale
- EQ-5D-5L
- Vital signs including BP, pulse rate, and temperature
- 12-lead ECG

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

- Assessment of concomitant medications including analgesics
- Clinical laboratory tests (only need to be done if they were not done within 72 hours of Day 1): serum chemistry, hematology, coagulation, hormone testing, liver function, and urinalysis
- Blood sampling for PK and PDy analysis
- Dispense study drug bottles

To be performed after the subject is dosed at the site:

- Record the dose (subject diary, source records, eCRF)

- 12-lead ECG to be performed 2 hours ± 10 minutes after dosing
- AE assessment

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

The following parameters are to be recorded:

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

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

Before any invasive procedures, the following parameters are to be recorded:

- Vital signs, including BP, pulse rate, and temperature
- 12-lead ECG

To be performed before the morning dose:

- Assessment of concomitant medications including analgesics
- Treatment compliance assessment
- Clinical laboratory tests: liver function, hematology
- Blood sampling for PK and PDy analysis

To be performed after the subject is dosed at the site:

- Record of the dose (subject diary, source records, eCRF)
- Blood sampling for PK analysis at various postdose time points (see Section 8.2)
- 12-lead ECG to be performed 2 hours ± 10 minutes after dosing
- AE assessment

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

The following parameters are to be recorded:

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

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

Before any invasive procedures, the following parameters are to be recorded:

- Vital signs including BP, pulse rate, and temperature

Other procedures to be performed:

- Treatment compliance assessment
- Assessment of concomitant medications including analgesics
- Physical examination
- Clinical laboratory tests: serum chemistry, hematology, liver function, serum pregnancy testing (as applicable)
- Blood sampling for PK and PDy analysis (see Section 8.2)
- Dispensation of study drug bottles
- AE assessment

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

The following parameters are to be recorded:

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

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

The following parameters are to be recorded:

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

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

The following parameters are to be recorded:

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

6.3.9. Cycle 3, Day 1 (C3D1; Week 9) ± 7 days

Before any invasive procedures, the following parameters are to be recorded:

- PROMIS Physical Function Scale
- EQ-5D-5L
- Vital signs including BP, pulse rate, and temperature

Other procedures to be performed:

- Treatment compliance assessment
- Assessment of concomitant medications including analgesics

- Clinical laboratory tests: serum chemistry, hematology, liver function, serum pregnancy testing (as applicable)
- Random postdose blood sampling for PK and PDy analysis
- Dispensation of study drug bottles
- AE assessment

6.3.10. Cycle 3, Day 15 (C3D15; Week 11) ± 7 days

The following parameters are to be recorded:

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

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

Before any invasive procedures, the following parameters are to be recorded:

- Vital signs, including BP, pulse rate, and temperature

To be performed within (±) 7 days of the visit:

- Treatment compliance assessment
- Assessment of concomitant medications including analgesics
- Physical examination
- MRI of the affected joint (with local assessment of progression status). The Investigator may request a centrally read blinded MRI to confirm progression, eg, if a subject's mid-study clinical profile or local radiological assessment indicates progression
- Photographic documentation of tumor
- Range-of-motion assessment of the affected joint

Other procedures to be performed:

- Clinical laboratory tests: serum chemistry, hematology, liver function, serum pregnancy testing (as applicable), and urinalysis
- Dispensation of study drug bottles
- AE assessment

6.3.12. Cycle 5, Day 1 (C5D1; Week 17) ± 7 days

Before any invasive procedures, the following parameters are to be recorded:

- PROMIS Physical Function Scale
- EQ-5D-5L

- Vital signs including BP, pulse rate, and temperature

Other procedures to be performed:

- Treatment compliance assessment
- Assessment of concomitant medications including analgesics
- Clinical laboratory tests: serum chemistry, hematology, liver function, serum pregnancy testing (as applicable)
- Random postdose blood sampling for PK and PDy analysis
- Dispensation of study drug bottles
- AE assessment

6.3.13. Cycle 6, Day 1 (C6D1; Week 21) ± 7 days

Before any invasive procedures, the following parameters are to be recorded:

- Vital signs including BP, pulse rate, and temperature

Other procedures to be performed:

- Treatment compliance assessment
- Assessment of concomitant medications including analgesics
- Clinical laboratory tests: serum chemistry, hematology, liver function, serum pregnancy testing (if applicable)
- Dispensation of study drug bottles
- AE assessment

6.3.14. Cycle 7, Day 1 Visit (C7D1; Week 25) ± 7 days

Before any invasive procedures, the following procedures have to be performed:

- PROMIS Physical Function Scale
- EQ-5D-5L
- Vital signs including BP, pulse rate, and temperature
- 12-lead ECG

To be performed within (±) 7 days of the visit:

- Treatment compliance assessment
- Assessment of concomitant medications including analgesics
- Surgical Assessment Questionnaire
- Weight
- Physical examination

- MRI of the affected joint (with local assessment of progression status). The Investigator may request a centrally read blinded MRI to confirm progression, eg, if a subject's mid-study clinical profile or local radiological assessment indicates progression
- Photographic documentation of tumor
- Range-of-motion assessment of the affected joint

Other procedures to be performed:

- Clinical laboratory tests: serum chemistry, hematology, coagulation, liver function, hormone testing, serum pregnancy testing (as applicable), and urinalysis
- AE assessment

The following procedures will be performed as part of the C7D1visit if the subject will continue the study:

After the subject is dosed at the site:

- Record the dose (subject diary, source records, eCRF)
- Dispensation of study drug bottles

6.3.15. Cycle 10+, Day 1 (C10+D1; Week 37+) ± 7 days

To be performed at C10+D1 ± 7 day and every 12 weeks thereafter (eg, C13, C16, C19).

Before any invasive procedures, the following parameters are to be recorded:

- PROMIS Physical Function Scale
- EQ-5D-5L
- Vital signs, including BP, pulse rate, and temperature

To be performed within (±) 7 days of the visit:

- Physical examination
- Treatment compliance assessment
- Assessment of concomitant medications, including analgesics
- MRI of the affected joint (with local assessment of progression status). The Investigator may request a centrally read blinded MRI to confirm progression, eg, if a subject's mid-study clinical profile or local radiological assessment indicates progression
- Photographic documentation of tumor
- Range-of-motion assessment of the affected joint

To be performed other procedures:

- Clinical laboratory tests: serum chemistry, hematology, liver function, serum pregnancy testing (if applicable)

- Dispensation of study drug bottles
- AE assessment

6.3.16. Post-treatment Visit (last dose + 28 days) ± 7 days

To be performed at 28 ± 7 days after the last dose of study drug.

Before any invasive procedures, the following parameters are to be recorded:

- PROMIS Physical Function Scale
- EQ-5D-5L
- Vital signs including BP, pulse rate, and temperature
- 12-lead ECG

The following procedures are to be performed within (±) 7 days of this visit:

- Assessment of concomitant medications including analgesics
- Surgical Assessment Questionnaire
- Weight
- Physical examination
- MRI of the affected joint (for subjects who withdraw from the study for reasons other than progression; local assessment of progression status will be recorded)
- Photographic documentation of tumor
- Third-party range-of-motion assessment of the affected joint

Other procedures to be performed:

- Clinical laboratory tests: serum chemistry, hematology, coagulation, liver function, hormone testing, serum pregnancy testing (if applicable), and urinalysis
- If surgical resection of the tumor is performed within 28 days after the last dose of study drug, obtain details and outcome of the surgery
- AE assessment
- For subjects terminating the study because of progression, document if they plan to undergo any new TGCT therapy, including surgery, during the 28 days period (± 7 days) after their last dose of study drug

6.3.17. End-of-Study or Early Termination Visit (last dose + 12 weeks) ± 7 days

This visit is scheduled 12 weeks ± 7 days after the last dose of study drug or before any new TGCT therapy, including surgery, whichever occurs first. It is scheduled for subjects who withdraw from the study for reasons other than progression.

- Concomitant medications

- If surgical resection of the tumor is performed within 12 weeks after the last dose of study drug, obtain details and outcome of the surgery
- MRI of the affected joint (with local assessment of progression status) is to be performed within (±) 7 days of the visit
- Photographic documentation of tumor
- Assess if the subject plans to begin any new TGCT therapy, including surgery
- Clinical laboratory tests: serum pregnancy testing (if applicable)
- AE assessment
- Terminate the subject from the study

6.3.18. Long Term Follow-up (every 6 months after end-of-study or early termination visit) ± 2 weeks

After completion of the end-of-study or early termination visit, the long term follow-up will be performed every 6 months by telephone contact. The questionnaire is provided in Section 16.5.

- Subject status

7. EFFICACY ASSESSMENTS

Subjects will be assessed for the efficacy endpoints listed in Section 3.1.2

7.1. Primary Efficacy Endpoint

The primary endpoint will be the proportion of subjects who achieve a CR or PR of pexidartinib based on RECIST 1.1 at Week 25 by centrally reviewed MRI scan.

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

- **Complete Response (CR)** — Disappearance of all tumors.
- **Partial Response (PR)** — At least a 30% decrease in the sum of diameters of target tumors, taking as reference the baseline sum diameters.
- **Progressive Disease (PD)** — 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 (SD)** — Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD.

CR 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. For the purpose of this protocol and in alignment with RECIST 1.1, determination of the tumor response status for each subject within 24 weeks treatment with respect to the primary efficacy endpoint is shown in Table 7.1.

To be considered a response, a tumor must meet the criteria for response and must have documented non-progression at Week 25. A tumor that achieves PR at Week 13 followed by neither sufficient shrinkage to qualify for CR nor sufficient increase to qualify for PD (ie, non-CR/non-PD/not evaluable [NE]) at Week 25 will be considered a responder for the primary efficacy endpoint.

Table 7.1: Definitions of Response for the Primary Endpoint

Time Point Response at Week 13 (C4D1 visit)	Time Point Response at Week 25 (C7D1visit)	Tumor Response Status (Primary efficacy endpoint)
CR or PR	CR	Response (CR)
CR or PR	PD	Nonresponse (PD)
PR	non-CR/non-PD/non-NE[a]	Response (PR)[b]
SD	CR or PR	Response (CR or PR)
SD	SD	Nonresponse (SD)
SD	PD	Nonresponse (PD)[c]
CR, PR, SD, or NE	NE	Nonresponse (NE)
PD	Any	Nonresponse (PD)
NE	CR or PR	Response (CR or PR)
NE	SD or PD	Nonresponse (SD or PD)

CR = complete response; NE = not evaluable; PD = progressive disease; PR = partial response; SD = stable disease

[a] Neither sufficient shrinkage to qualify for CR nor sufficient increase to qualify for PD, taking as reference the nadir at Week 13.

[b] A tumor that has achieved the criteria of PR will be considered an ongoing PR until progressive disease is objectively documented.

[c] To be considered SD, the tumor must achieve the criteria for SD at the Week 25 visit; shorter-duration SD will not be considered SD at the end of Week 24.

For the entire study, centralized review of the MRI scans will be performed by readers blinded to study subject information according to procedures outlined in a separate MRI Imaging Charter. Scans will be obtained according to the MRI Imaging Charter. The Imaging Charter for this study describes the image acquisition standards and methodology to be used as well as the standards for image interpretation.

7.1.1. Tumor Imaging

MRI (Noncontrast or follow the standard operation of the sites) of the affected joint will be performed at the study visits indicated in the Schedule of Assessment (Table 16.3). All MRI scans will be centrally read. Local evaluation of radiological response, stable disease (SD) or PD according to RECIST 1.1 will be recorded in the eCRF. The central MRI assessment report of progression status will not be provided unless requested. The Investigator will follow procedures (including instructions on proper imaging technique, and labeling) outlined in a separate MRI Procedure Manual. The results of the baseline, centrally read MRI scan will be used to qualify a subject, and all subsequent MRI scans will be read centrally.

If disease progression is indicated clinically or by local radiological assessment according to RECIST 1.1 at or after Week 13 but before Week 25, the Investigator may request a central review for evaluation of disease progression. If a central reading confirms RECIST 1.1 defined

disease progression, subject will be discontinued from the study unless the Investigator and the DS's Medical Monitor judge that the subject would potentially benefit from continued treatment with pexidartinib.

During the study, if indicated, Investigators should request confirmation of radiological disease progression by central read. Otherwise, central reading of MRI scans may be performed during or after the subject has completed the study. Details for MRI scan reads are outlined in the MRI Procedure Manual.

Subjects who terminate the study because of radiological disease progression will NOT have a follow-up MRI at their post-treatment visit.

7.2. Secondary Efficacy Endpoints

The following evaluations comprise the secondary endpoints:

- Proportion of subjects who achieve a CR or PR of pexidartinib based on TVS at Week 25 by centrally reviewed MRI scan
- Mean change from baseline in range of motion of the affected joint, relative to a reference standard for the same joint, at the Week 25
- Mean change from baseline score in the PROMIS Physical Function Scale at the Week 25
- Best overall response (CR or PR) of pexidartinib based on RECIST 1.1 and TVS by centrally reviewed MRI scan
- Duration of response (CR or PR) of pexidartinib based on RECIST 1.1 and TVS by centrally reviewed MRI scan

TVS is a semi-quantitative MRI scoring system that describes tumor mass and is an extension of the 4 point synovitis scale of the well-established and widely used multifeature score (Rheumatoid Arthritis MRI Score), originally developed for rheumatoid arthritis[10] and whole-organ MRI score (WORMS), originally developed for osteoarthritis.[11] The extended scale, the TVS, will be based on 10% increments of the estimated volume of the maximally distended synovial cavity or tendon sheath involved. Thus, a tumor that is equal in volume to that of a maximally distended synovial cavity or tendon sheath will be scored 10, whereas a tumor that is 70% of that volume will be scored 7, a tumor that is twice the volume of the maximally distended synovial cavity or tendon sheath will be scored 20, and so on. A score of "0" means no evidence of tumor.

Individual subject outcomes by TVS will be classified according to the following criteria inspired by RECIST 1.1:

- Complete response: Lesion completely gone.
- PR: ≥ 50% decrease in volume score relative to baseline.
- PD: ≥ 30% increase in volume relative to lowest score during the study whether at baseline or some other visit. In the case of limited residual disease, the increase in tumor volume must also be unequivocally larger.

- SD: Does not meet any of the prior criteria based on score during study.

The cutoffs of 50% for PR and +30% for PD were developed in consultation with clinical experts. This magnitude of reduction was observed in a majority of evaluable subjects with TGCT from the Phase 1 of pexidartinib (Section 1.3.1). The tumor response status on this endpoint within 24 weeks treatment is determined in a way similar to that for the primary efficacy endpoint (Table 7.1). To minimize bias and reduce variability, MRIs for primary endpoint and secondary endpoints will be read centrally in a blinded manner for RECIST 1.1- and TVS-based responses according to the separate MRI Imaging Charter.

Treatment effects on physical function will be assessed by an objective range of motion assessment performed by a qualified assessor, such as an orthopedic surgeon or a physical therapist blinded and when possible, to study drug name and to study protocol. This assessment uses standard goniometers and has been standardized according to American Medical Association disability criteria.[12] Details of this analysis are described in Section 10.5.

The PROMIS Physical Functioning items addresses symptoms of immobility. The first scale is applicable to subjects with lower-extremity tumors, and the second scale applies to subjects with upper-extremity tumors. Since tumors can be found in either the upper or lower extremities, the PROMIS Physical Functioning items provides the opportunity to include measurement of both sites in a way that is not possible with other similar instruments (eg, the Western Ontario and McMaster Universities Osteoarthritis Index for TGCT, which only measures functioning in the lower extremities).

7.2.1. Range of Motion Assessment

Range of motion will be assessed by a qualified assessor, such as an orthopedic surgeon or a physical therapist, using goniometers according to a standardized method based on American Medical Association disability criteria.[12] Measurements will be recorded in degrees. Details of the measurement procedure for each joint will be provided in the manual.

7.2.2. PROMIS Physical Function Scale

At the Week 25 visit, subjects will complete via the PROMIS Physical Function Scale at the indicated study visits in the Schedule of Assessment (Table 16.3). Physical function items relevant to the assessment of lower and upper limb function are to be selected from the PROMIS physical function item bank (Section 16.2). Items assessing lower limb function will be administered to subjects with the lower extremity tumors, and items assessing upper limb function will be administered to subjects with upper extremity tumors. The results from both sets of items will be combined and analyzed together.

7.3. Exploratory Efficacy Endpoint

Exploratory efficacy endpoints to be analyzed at appropriate time points include:

- Proportion of subjects who achieve a CR or PR of pexidartinib based on RECIST 1.1 at Week 25 by locally reviewed MRI scan
- Proportion of subjects who achieve a CR or PR of pexidartinib based on modified RECIST 1.1-SSD at Week 25 by centrally reviewed MRI scan

- Mean change from baseline score in the EQ-5D-5L at the Week 25
- Best overall response (CR or PR) of pexidartinib based on RECIST 1.1 by locally reviewed MRI scan
- Duration of response (CR or PR) of pexidartinib based on RECIST 1.1 by locally reviewed MRI scan
- Duration of response (CR or PR) of pexidartinib based on modified RECIST 1.1-SSD by centrally reviewed MRI scan
- Photographic documentation of tumor size change
- Results of the Surgical Assessment Questionnaire
- PDy of plasma CSF-1 activity
- Long term subject status after the end-of-study or early termination visit

7.3.1. EuroQol Five-Dimensional Descriptive System

At the Week 25 visit, subjects will complete via the EQ-5D-5L at the indicated study visits in the Schedule of Assessment (Table 16.3).

The EQ-5D-5L is a preference-based general health status or health-related quality of life instrument consisting of two parts. The first part comprises five domains (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) each of which can have five levels ranging from no problems through profound difficulties. Accordingly, 3125 potential health profiles can be generated to which public preferences or utilities are applied. These data can subsequently be used in an economic evaluation or cost-utility analysis. The second part of the EQ-5D-5L is a Visual Analogue Scale on which the subject rates their current health, with 0 representing the "worst health you can imagine" and 100 representing the "best health you can imagine."

7.3.2. Photographic Documentation of Tumor size Change

The photographic documentation will be collected to assess the tumor size change by photo if applicable.

7.3.3. Surgical Assessment Questionnaire

The surgical assessment questionnaire (Section 16.4) will be completed by a qualified individual (eg, orthopaedic oncologist) to assess the surgical status of the subject at the Screening visit and at time points shown in the Schedule of Assessment.

7.4. Appropriateness of Selected Efficacy Assessments

The appropriateness of selected efficacy endpoints is described in Section 7.1 and Section 7.2.

8. PHARMACOKINETIC/PHARMACODYNAMIC/ PHARMACOGENOMIC ASSESSMENTS

Subjects will be assessed for the PK and PDy endpoints.

8.1. Pharmacodynamic Assessment

Plasma for PDy biomarker (CSF-1 activity) will be collected once per day on the same days when PK blood sample(s) are drawn (eg, predose) and will be analyzed for markers of pexidartinib exposure.

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

8.2. Pharmacokinetic Assessment

PK sampling will be performed at the study visits indicated in the Schedule of Assessment (Table 16.3). Each site must choose one of the schedules for each subject and must adhere to the selected schedule (Table 8.1) for the duration of the study:

Table 8.1: Pharmacokinetic Schedules

Visit	Schedule 1	Schedule 2
Week 1 C1D1	Predose	Predose
Week 3 C1D15	Predose 0.5 h postdose (± 10 min) 1 h postdose (± 15 min) 2 h postdose (± 15 min) 4 h postdose (± 20 min) 6 h postdose (± 20 min)	Predose Postdose: Between 1 h and 3 h
Week 5 C2D1	Random postdose	Random postdose
Week 9 C3D1	Random postdose	Random postdose
Week 17 C5D1	Random postdose	Random postdose

h = hour(s); min = minute(s)

Subjects must be told to NOT take the morning dose of study drug at the C1D15 visit. Instead, they must be told to bring their bottle of study drug to the site and follow dosing instruction by the site staff.

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

Blood samples of approximately 3 mL for PK analyses will be collected at the time points specified in Table 8.1.

The PK analyses will be performed on the PK analysis set (see Section 10.7). Detailed instructions on collection, processing, handling, storage, and sample shipment are provided in the Laboratory Manual.

9. SAFETY EVALUATION AND REPORTING

9.1. Adverse Event Collection and Reporting

All AEs (see Section 9.4.1 for definitions) occurring after the subject signs the ICF and through the post-treatment visit (28 ± 7 days after the last dose of study drug), whether observed by the Investigator or reported by the subject, will be recorded on the AE eCRF page. Medical conditions (including laboratory values/vital signs that are out of range) that were diagnosed or known to exist prior to informed consent will be recorded as part of medical history.

All AEs and serious adverse events (SAEs) are to be reported according to the procedures in Section 9.5.

All clinical laboratory results, vital signs, hormone testing results and ECG results or findings should be appraised by the Investigator to determine their clinical significance. Isolated abnormal clinical laboratory results, hormone testing 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 subject. AEs may be directly observed, reported spontaneously by the subject or by questioning the subject at each study visit. Subjects should be questioned in a general way, without asking about the occurrence of any specific symptoms. The Investigator must assess all AEs to determine seriousness, severity, and causality, in accordance with the definitions in Section 9.4.1. 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. In addition, any serious untoward event that may occur subsequent to the reporting period that the Investigator assesses as related to study drug must also be reported and managed as an SAE.

The Investigator must follow subjects 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. Assessment of Safety Endpoint

Safety endpoints include physical examination, vital signs, 12-lead ECG, AE reports, serum chemistry, hematology, coagulation tests, urinalysis, hormone testing (as applicable), and concomitant medications. All TEAEs will be graded according to the National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 5.0.

9.3. Adverse Events of Special Interest

9.3.1. Liver enzyme elevations and Bilirubin elevation

- Elevation of ALT and/or AST greater than 3 × ULN
- Elevation of ALP greater than 2 × ULN with elevation of GGT greater than 2 × ULN
- Elevation of total bilirubin greater than ULN
- Elevation of direct bilirubin greater than ULN
- 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 ≥ 3 × ULN and total bilirubin > 2 × ULN) that may occur simultaneously or at different time points during the study

If the subject meet the criteria described in Table 5.2 due to liver enzyme abnormalities, the subject 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 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 laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product (International Council for Harmonisation [ICH] E2A Guideline. Clinical Safety Data Management: Definitions and Standards for Expedited Reporting, Oct 1994).[13]

It is the responsibility of Investigators, based on their knowledge and experience, to determine those circumstances or abnormal laboratory findings which should be considered as 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).[13]

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

Note:

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

9.4.3. Severity Assessment

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

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

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 subject/event outcome at the time of the event. For example, the NCI-CTCAE Grade 4 (life-threatening consequences; urgent intervention indicated) is assessed based on unique clinical descriptions of severity for each AE, and these criteria may be different from those used for the assessment of AE seriousness. An AE assessed as Grade 4 based on the NCI-CTCAE 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 subject's clinical state or other factors (eg, disease under study, concurrent diseases, and concomitant medications).

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

9.4.5. 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 increased.
- Not Applicable: Subject died, study treatment had been completed prior to reaction/event, or reaction/event occurred prior to start of treatment.

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 subject fully recovered from the AE with no residual effect observed.
- Recovered/Resolved with Sequelae
  - The residual effects of the AE are still present and observable.
  - 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. Adverse Events Reporting–Procedure For Investigators

All AEs and SAEs will be reported in the eCRF.

The following types of events should be reported by the Investigator on the SAE form of eCRF or on a Serious Adverse Event Report (SAVER) Form in case of eCRF downtime within 24 hours of awareness:

- SAEs (see Section 9.4.2)
- Adverse Event of Special Interest (see Section 9.3)
  - Elevation of ALT and/or AST greater than 3 × ULN
  - Elevation of ALP greater than 2 × ULN with elevation of GGT greater than 2 × ULN
  - Elevation of total bilirubin greater than ULN
  - Elevation of direct bilirubin greater than ULN
  - 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 × ULN and total bilirubin > 2 × ULN) that may occur simultaneously or at different time points during the study
- Overdose (see Section 9.8)

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 DS 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.

Please call the local SAE Hotline (see medical monitoring plan) or your study monitor for any questions on SAE reporting.

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

DS 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 DS studies of the investigational product, as appropriate per local reporting requirements. DS and/or designee will comply with any additional local safety reporting requirements.

In the China, upon receipt of DS's notification of SUSARs that occurred with the investigational product, unless delegated to DS, 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

DS must be notified of any female subject or any male subject whose female partner becomes pregnant while receiving or within 90 days 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 subject or a male subject's female partner using the Exposure In Utero (EIU) Reporting Form. Please contact your study monitor to receive the EIU Reporting Form upon learning of a pregnancy. The Investigator should make every effort to follow the subject until completion of the pregnancy and complete the EIU Reporting Form with complete pregnancy outcome information, including normal delivery and induced abortion. The adverse pregnancy outcome, either serious or 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 subject, the EIU Reporting Form (or SAE form if associated with an adverse outcome) must be completed with the subject's enrollment number, initials, and date of birth, and details regarding the female partner should be entered in the narrative section.

9.8. Overdose

Overdose, defined as the accidental or intentional administration of any dose of pexidartinib that is considered both excessive and medically important. All occurrences of overdose must be reported to (CRO or Sponsor) within 24 hours of awareness. Overdose could be reported via

[SAVER/overdose] form or eCRF. An "excessive and medically important" overdose includes any overdose in which either a SAE, a non-SAE, or no AE occurs and is considered by the Investigator as clinically relevant, i.e. poses an actual or potential risk to the subject. Details of the overdose including pexidartinib dosage, clinical course, associated AEs, and outcome must be captured in the Narrative form of the eCRF within electronic data capture (EDC).

9.9. Clinical Laboratory Evaluations

Clinical laboratory evaluations will be performed in local laboratory at the study visits indicated in the Schedule of Assessment (Table 16.3). For clinical 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, coagulation, and hormone testing 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 (creatinine clearance)**	

CO_2 = Carbon dioxide; HDL = high density lipoprotein; LDL = low density lipoprotein
* Fasting is recommended but not required.
**CLcr will be calculated using following formula (Cockcroft-Gault).
CLcr = {((140 – age) × weight (kg))/(72 × serum creatinine (mg/dl))} (× 0.85 if female).

Liver function Tests

• Alkaline phosphatase	• Total bilirubin
• AST	• Direct bilirubin
• ALT	• GGT

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

Hematology

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

Hepatitis Panel

Hepatitis B virus surface antigen test and hepatitis C virus antibody test

Coagulation

Prothrombin time, activated partial thromboplastin time, and INR

Hormone Testing

Females	Males
• FSH	• FSH
• LH	• LH
• Progesterone	• Testosterone
• Estradiol	

FSH = follicle stimulating hormone; LH = luteinizing hormone

Urinalysis (dipstick and microscopic analysis)

Urine samples will be obtained for analysis of the following parameters:

• pH	• Ketones/acetone
• Protein/albumin	• Hemoglobin/blood
• Glucose/sugar	• Red blood cells, white blood cells, epithelial cells, bacteria, casts, crystals
• Nitrites	

Others

Serum sample must be collected for AMA at Screening and once severe hepatotoxicity is observed (Section 5.4).

9.10. 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 Assessment (Table 16.3).

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

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

9.11. Vital Signs

Vital signs, including systolic/diastolic BP, pulse rate and temperature will be measured in accordance with institutional standards and generally must 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 Assessment (Table 16.3). Height will be measured at the Screenings visit only.

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

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

9.12. Electrocardiograms

A standard 12-lead ECG will be obtained at the study visits indicated in the Schedule of Assessment (Table 16.3).

Subjects should rest in the supine position for at least 5 minutes 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 must be reviewed, signed, and dated promptly by a qualified Investigator (or Investigator's assistant, 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, subjects must be told NOT to take the morning dose of study drug; instead, they must 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.

9.13. Examinations

The examination will be performed by a qualified individual such as the Investigator at the study visits indicated in the Schedule of Assessment (Table 16.3).

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.

9.14. Safety Monitoring

9.14.1. Safety Monitoring Committee

A safety monitoring committee (SMC) to assess liver toxicity will be established and will be responsible for safeguarding the interests of study subjects, assessing the safety of the interventions during the study, and monitoring the overall conduct of the study. The SMC will

also evaluate progress of the study and other relevant information, and make recommendations about continuing, modifying, or stopping the study. A separate SMC Charter will define the SMC membership, its roles and responsibilities, and the process for providing feedback to the DS.

9.14.2. Hepatic Adjudication Committee

An external hepatic adjudication committee (HEAC) is used for evaluating hepatic AEs for this study. Details on the membership, responsibilities, and working procedures of the external HEAC will be described in the separate charter. This additional data collection will cover a more in-depth, relevant medical history, diagnostic evaluation, treatment, and outcome of the event. Adjudication of hepatic events will be based on evaluation of eCRFs and source documents, including, but not limited to, liver ultrasound, other imaging of the liver, and liver biopsy.

10. STATISTICAL METHODS

10.1. Analysis Sets

10.1.1. Enrolled Analysis Set

The enrolled analysis set will include all subjects who sign the ICF and are enrolled in the study.

10.1.2. Full Analysis Set/Safety Analysis Set

The Full analysis set (FAS)/safety analysis set will include all subjects who received at least 1 dose of pexidartinib.

10.1.3. Per-protocol Analysis Set

Not Applicable.

10.1.4. Pharmacokinetic Analysis Set

The PK analysis set will include all subjects in the enrolled analysis set who received at least 1 dose of pexidartinib and had measurable plasma concentrations of pexidartinib.

10.1.5. Pharmacokinetic Analysis Set for Noncompartmental Analysis

The PK analysis set for noncompartmental analysis will include all subjects in the PK analysis set who chose Schedule 1 in clinical sites.

10.2. 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, subjects who do not provide data for the responder endpoint will be considered nonresponders, ie, assigned to the less favorable outcome for the endpoint. Subjects who do not have the Week 25 MRI assessment, for example, those who discontinue the study without Week 25 assessment will be considered nonresponders.

10.3. General Statistical Considerations

The data cutoff for the primary analysis will occur after all subjects have either discontinued the study or completed at least Week 25 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 post-treatment or the ratio of post-treatment to baseline will include only those subjects with both baseline and post-treatment measurements. The last nonmissing value of a variable taken before the first dose of study drug will be used as the baseline value, unless otherwise specified. In general, missing or dropout data will not be imputed for the purpose of data analysis, unless otherwise specified.

For the primary efficacy endpoint and secondary efficacy endpoints with the exception of duration of response, point estimate and accompanying 95% CI will be computed. For duration

of response, Kaplan-Meier product limit methodology will be utilized to provide estimates, including those for the median and 25th and 75th percentiles.

10.4. Study Population Data

Subject disposition will be summarized for subjects in the enrolled analysis set. The total number of subjects 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.

10.5. Efficacy Analyses

10.5.1. Primary Efficacy Analyses

The primary endpoint will be the proportion of subjects who achieve a CR or PR of pexidartinib based on RECIST 1.1 at Week 25 by centrally reviewed MRI scan (see Section 7.1). 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.

10.5.2. Secondary Efficacy Analyses

The secondary efficacy endpoints to be analyzed at Week 25 include:

- Proportion of subjects who achieve a CR or PR of pexidartinib based on TVS at Week 25 by centrally reviewed MRI scan
- Mean change from baseline in range of motion of the affected joint, relative to a reference standard for the same joint, at the Week 25
- Mean change from baseline score in the PROMIS Physical Function Scale at the Week 25

Subjects who do not provide data for the endpoint will be considered to be non-responders (TVS).

The estimate of the proportion of TVS responders (ie, those who achieve a CR or PR based on TVS criteria) and 95% CI at Week 25 will be calculated.

Other secondary endpoints will be also summarized with point estimates and 95% CIs.

For the endpoint of range-of-motion, raw measurements of the affected joint will be performed using a goniometer and expressed in degrees (Section 7.2.1). The value for a given joint will be normalized to a reference standard, ie, full range of motion for the same joint, to provide a relative value. The reference standard will be derived from American Medical Association disability criteria.[12]

Duration of response will also be analyzed as a secondary endpoint and will be summarized for responders based on (i) RECIST 1.1 and (ii) TVS. Duration of response is defined from the date of the first recorded response to the first date of documented disease progression. For subjects who do not have radiological progression, the duration of response will be censored. The Kaplan-Meier product limit method will be used to compute the estimate and 95%CI of the

median and 25th and 75th 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 months will also be provided.

The percentage and 95% CI will be provided for the best overall response in the order of CR, PR, SD, PD, and NE.

10.5.3. Exploratory Efficacy Analyses

Exploratory efficacy endpoints to be analyzed at Week 25, with the exception of duration endpoints or otherwise indicated, include:

- Results of the Surgical Assessment Questionnaire
- Response based on the change in the SSD of the tumor on MRI
- Duration of response based on MRI and modified RECIST 1.1-SSD
- Mean change from baseline score in the EQ-5D-5L at Week 25
- Summary of the long term subject status during the follow-up period

10.5.4. Subgroup Analyses

The primary endpoint will be also analyzed in the following subgroups of the FAS:

- Subjects with disease located in large joints (shoulder, elbow, hip, or knee)
- Subjects with disease located in the knee
- Subjects with lower extremity tumors
- Subjects with upper extremity tumors
- Subjects at sites in China
- Subjects at sites in Taiwan

10.6. Pharmacodynamic/Biomarker Analyses

Plasma will be analyzed for PDy marker, CSF-1 activity. No formal statistical analysis of PDy endpoint will be performed. Pharmacodynamic data from each assay will be listed and biological activity will be described. Blood sample collected at specified time points will be analyzed for genes possibly related to efficacy and safety of pexidartinib.

10.7. Pharmacokinetics and Exposure-Response Analyses

10.7.1. Noncompartmental Pharmacokinetic Analyses

The PK analyses will be performed on the PK analysis set. Plasma-concentration time data for pexidartinib and ZAAD-1006a will be summarized by visit and time using descriptive statistics.

Plasma-concentration data of pexidartinib and ZAAD-1006a on C1D15 (Week 3) will be analyzed for the PK analysis set for noncompartmental analysis using standard

noncompartmental methods. Primary PK parameters are area under the plasma-concentration-time curve from time 0 h to 6 h (AUC6h), peak drug concentration (Cmax), and time of maximum observed concentration (Tmax). The PK parameters of pexidartinib will be listed for each subject and summarized using descriptive statistics.

10.7.2. Population Pharmacokinetic Analyses

Plasma-concentration data from these samples will be analyzed using a population pharmacokinetic (PopPK) approach using nonlinear mixed effects modeling by pooled with other studies data to assess and characterize the inter- and intra-subject variability in PK and to identify significant covariates. These results will be analyzed and reported separately from the clinical study results.

10.7.3. Exposure-Response Analyses

Bayesian individual exposures of pexidartinib from the PopPK analysis will be used to explore relationships between exposure metrics and biomarkers and safety and efficacy endpoints. These analyses will be summarized in a separate report.

10.8. 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 Drug 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-subject listing will be provided for those subjects who experience an SAE, including death, or experience an AE associated with early withdrawal from the study or study drug.

10.8.1. Adverse Event Analyses

TEAEs are AEs that occur, having been absent before the first dose of study drug, or have worsened in severity after the initiating the study drug. TEAEs will be coded using MedDRA and assigned grades based on NCI-CTCAE version 5.0. The number and percentage of subjects reporting TEAEs will be tabulated by the worst CTCAE grade, SOC, and PT. Similarly, the number and percentage of subjects reporting treatment-emergent SAEs will be tabulated, as well as TEAEs leading to discontinuation of study drug.

A by-subject 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.

10.8.2. 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 post-treatment values and the values at the end of treatment visit.

Abnormal clinical laboratory results will be graded according to NCI-CTCAE version 5.0, if applicable, and the grade will be presented in a by-subject data listing. A shift table, presenting the 2-way frequency tabulation for baseline and the worst post-treatment value according to the 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.

10.8.3. 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 for the maximum and minimum post-treatment values and the values at the end of treatment visit.

10.8.4. 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 subjects with ECG interval values meeting the criteria will be tabulated (eg, QTc $\leq$ 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 post-treatment evaluations will be summarized. ECG data will also be presented in the data listings.

10.8.5. Physical Examination Analyses

Physical examination data will be listed.

10.8.6. Concomitant Medication Analyses

Concomitant medications will be coded using the World Health Organization drug dictionary (most recent version). Number and percentage of subjects taking concomitant medications will be summarized for the safety analysis set.

10.9. Other Endpoint Analysis

Not applicable.

10.10. Interim Analyses

No formal interim analysis is planned.

10.11. Sample Size Determination

Planned sample size is approximately 35 subjects. The 95% CIs for some ORR values based on 35 subjects are as follows:

N	Number of responders	ORR	95% CI
35	9	25.7%	(12.5%, 43.3%)

35	10	28.6%	(14.6%, 46.3%)
35	11	31.4%	(16.9%, 49.3%)
35	12	34.3%	(19.1%, 52.2%)
35	13	37.1%	(21.5%, 55.1%)
35	14	40.0%	(23.9%, 57.9%)
35	15	42.9%	(26.3%, 60.6%)
35	16	45.7%	(28.8%, 63.4%)

10.12. Statistical Analysis Process

The clinical study will be analyzed by DS or its agent/CRO followed by 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 subject disposition, demographic and baseline characteristics, study drug exposure, and prior and concomitant medications. The SAP will also include a description of how missing, unused, and spurious data will be addressed.

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

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

11. DATA INTEGRITY AND QUALITY ASSURANCE

The Investigator/investigational study sites 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.

11.1. Monitoring and Inspections

DS/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, CRFs, source data, and other pertinent documents).

The verification of adherence to the protocol; completeness, accuracy, and consistency of the data; and adherence to ICH GCP and local regulations on the conduct of clinical research will be accomplished through a combination of onsite visits by the monitor and review of study data remotely. The frequency of the monitoring visit will vary based on the activity at each study site. The monitor is responsible for inspecting the eCRFs and ensuring completeness of the study essential documents. The monitor should have access to subject'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 any deviations from the protocol, Standard Operating Procedures, GCP and applicable regulations to the Investigator and will ensure that appropriate action (s) designed to prevent recurrence of the detected deviations is taken and documented.

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

In accordance with ICH GCP and the DS's audit plans, this study site may be selected for audit by representatives from DS. 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, DS shall be notified immediately.

11.2. Data Collection

DS or its designee will provide the study sites with secure access to and training on the EDC application, sufficient to permit site personnel to enter or correct information in the eCRFs for the subjects for which they are responsible.

eCRFs will be completed for each study subject. It is the Investigator's responsibility to ensure the accuracy, completeness, clarity, and timeliness of the data reported in the subject'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 subject for which he or she is responsible.

DS 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.

11.3. Data Management

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

To ensure the quality of clinical data across all subjects and sites, a Clinical Data Management review will be performed on subject data according to specifications given to DS or DS 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, subject data will be checked for consistency, completeness, and any apparent discrepancies.

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

SAE in the clinical database will be reconciled with the safety database. All AEs will be coded using MedDRA.

11.4. Study Documentation and Storage

Source documents are original documents, data, and records from which the subject's eCRF data are obtained. These include, but are not limited to, hospital records, clinical and office charts, laboratory and pharmacy records, diaries, microfiches, X-rays, and correspondence. 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 subjects, source documents, monitoring visit logs, data correction forms, eCRFs, inventory of study drug, regulatory documents (eg, protocol and amendments, IRB/EC correspondence and approvals, approved and signed ICFs, Investigator's Agreement, clinical supplies receipts, distribution and return records), and other DS 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, DS must be notified in writing and be given the opportunity to further store such records.

11.5. Record Keeping

The Investigator and study staff are responsible for maintaining a comprehensive and centralized filing system (Trial Master File) of all study-related (essential) documentation. These documents should be suitable for inspection at any time by representatives from DS and/or applicable regulatory authorities. Essential documents contained in the Trial Master File include:

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

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

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

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

No study document should be destroyed without prior written agreement between DS 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 DS in writing of the new responsible person and/or the new location.

12. FINANCING AND INSURANCE

12.1. Finances

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

12.2. Reimbursement, Indemnity, and Insurance

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

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

13. PUBLICATION AND PUBLIC DISCLOSURE OF CLINICAL TRIAL INFORMATIONP

DS is committed to meeting the highest standards of publication and public disclosure of information arising from clinical trials sponsored by the company. We will comply with US, EU, and Japanese policies for public disclosure of the clinical trial protocol and clinical trial results, and for sharing of clinical trial data. We follow the principles set forward in "Good Publication Practice for Communicating Company-Sponsored Medical Research (GPP3)", and publications will adhere to the "Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals" established by the International Council of Medical Journal Editors (ICMJE).

In order to ensure that we are in compliance with the public disclosure policies and the ICMJE recommendations, and to protect proprietary information generated during the study, all publications (manuscripts, abstracts, or other public disclosure) based on data generated in this study must be accepted, reviewed, and approved in writing by the sponsor prior to submission.

14. ETHICS AND STUDY ADMINISTRATIVE INFORMATION

14.1. Compliance Statement, Ethics, and Regulatory Compliance

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

14.2. Subject Confidentiality

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

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

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

14.3. Informed Consent

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

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

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

If the subject cannot read, then according to ICH GCP Guideline (Section 4.8.9), an impartial witness must be present during the entire informed consent discussion. This witness must sign the ICF after the subject has consented to the subject's participation and, if possible, signed the

ICF. By signing the ICF, the witness attests that the information in the ICF and any other written information was adequately explained to and apparently understood by the subject and that informed consent was freely given by the subject.

Suggested model text for the ICF for the study and any applicable subparts (genomic, PK, etc.) are provided in the DS'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 DS.

14.4. Regulatory Compliance

The study protocol, subject ICF, the IB, any written instructions to be given to the subject, available safety information, subject recruitment procedures (eg, advertisements), information about payments and compensation available to the subjects, and documentation evidencing the Investigator's qualifications should be submitted to the EC or IRB for ethical review and approval according to local regulations, prior to the study start. The written approval must 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 Sponsor will appoint a Coordinating Investigator. Among other possible duties, the Coordinating Investigator will be responsible for reviewing and approving the Final Clinical Study Report and testifying to the accuracy of the description of the study conduct. Because the Coordinating Investigator should have personal knowledge of the conduct of the study, he or she will normally be chosen from among those Investigators who have enrolled and treated at least one subject. However, where an Investigator has special knowledge of the field or of the trial, the Coordinating Investigator can be chosen prior to enrolment of the first subject. In all cases, the Coordinating Investigator must be chosen prior to locking the database.

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

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

In the event of any prohibition or restriction imposed (eg, clinical hold) by an applicable Regulatory Authorities in any area of the world, or if the Investigator is aware of any new information which might influence the evaluation of the benefits and risks of the study drug, DS must be informed immediately.

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

14.5. Protocol Deviations

The Investigator must conduct the study in compliance with the protocol agreed to by DS and, if required, by the regulatory authorities, 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 subject. DS must be notified of all intended or unintended deviations to the protocol (eg, inclusion/exclusion criteria, dosing, missed study visits) on an expedited basis.

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

If a subject was ineligible or received the incorrect dose or study treatment, and had at least one administration of the study drug, for example, data should be collected for safety purposes, and the DS's medical monitor or designee should be informed immediately.

The Investigator must notify the IRB/IEC of deviations from the protocol in accordance with local procedures.

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

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

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

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

14.7. Protocol Amendments

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

A 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. DS 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 subject safety.

14.8. Study Termination

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

DS 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 DS determines such action is needed, then DS will discuss this with the Investigator (including the reasons for taking such action) at that time. When feasible, DS will provide prior notification to the Investigator of the impending action prior to its taking effect.

DS 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 DS. In addition, arrangements will be made for return of all unused study drugs in accordance with the DS'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 DS.

15. REFERENCES

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16. APPENDICES

16.1. List of Common CYP3A Inhibitors and Inducers

Strong Inhibitors	Moderate inhibitors	Strong Inducers
• Boceprevir	• Aprepitant	• Carbamazepine
• Clarithromycin	• Ciprofloxacin	• Enzalutamide
• Cobicistat	• Conivaptan	• Mitotane
• Danoprevir and ritonavir	• Crizotinib	• Phenytoin
• Elvitegravir and ritonavir	• Cyclosporine	• Rifampin
• Grapefruit juice	• Diltiazem	• St. John's wort
• Idelalisib	• Dronedarone	• Apalutamide
• Indinavir and ritonavir	• Erythromycin	
• Itraconazole	• Fluconazole	
• Ketoconazole	• Fluvoxamine	
• Lopinavir and ritonavir	• Imatinib	
• Nefazodone	• Tofisopam	
• Nelfinavir	• Verapamil	
• Paritaprevir and ritonavir and (ombitasvir and/or dasabuvir)		
• Posaconazole		
• Ritonavir		
• Saquinavir and ritonavir		
• Telaprevir		
• Telithromycin		
• Tipranavir and ritonavir		
• Troleandomycin		
• Voriconazole		

Source: Food and Drug Administration (FDA) web site: Drug Development and Drug Interactions: Table of Substrates, Inhibitors and Inducers (3 Dec 2019). Available from: https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers

16.2. PROMIS Physical Function Scale

PROMIS Item Bank v. 1.2 – Physical Functioning (Lower Extremity)

Please respond to each item by marking one box per row.

		Without any difficulty	With a little difficulty	With some difficulty	With much difficulty	Unable to do
PFA23	Are you able to go for a walk of at least 15 minutes?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFA16r1	Are you able to dress yourself, including tying shoelaces and buttoning up your clothes?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
		Not at all	**Very little**	**Somewhat**	**Quite a lot**	**Cannot do**
PFB54	Does your health now limit you in going OUTSIDE the home, for example to shop or visit a doctor's office?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFA4	Does your health now limit you in doing heavy work around the house like scrubbing floors, or lifting or moving heavy furniture?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
		Without any difficulty	**With a little difficulty**	**With some difficulty**	**With much difficulty**	**Unable to do**
PFA12	Are you able to push open a heavy door?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFA14r1	Are you able to carry a heavy object (over 10 pounds/5 kg)?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
		Not at all	**Very little**	**Somewhat**	**Quite a lot**	**Cannot do**
PFB1	Does your health now limit you in doing moderate work around the house like vacuuming, sweeping floors or carrying in groceries?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFA5	Does your health now limit you in lifting or carrying groceries?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
		Without any difficulty	**With a little difficulty**	**With some difficulty**	**With much difficulty**	**Unable to do**

		Without any difficulty	With a little difficulty	With some difficulty	With much difficulty	Unable to do
PFA21	Are you able to go up and down stairs at a normal pace?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFA42	Are you able to carry a laundry basket up a flight of stairs?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFA10	Are you able to stand for one hour?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
		Not at all	**Very little**	**Somewhat**	**Quite a lot**	**Cannot do**
PFA3	Does your health now limit you in bending, kneeling, or stooping?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
		Without any difficulty	**With a little difficulty**	**With some difficulty**	**With much difficulty**	**Unable to do**
PFA13	Are you able to exercise for an hour?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1

PROMIS Item Bank v. 1.2 – Physical Functioning (Upper Extremity)

Please respond to each item by marking one box per row.

		Without any difficulty	With a little difficulty	With some difficulty	With much difficulty	Unable to do
PFB34	Are you able to change a light bulb overhead?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFA16r1	Are you able to dress yourself, including tying shoelaces and buttoning up your clothes?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
		Not at all	**Very little**	**Somewhat**	**Quite a lot**	**Cannot do**
PFB54	Does your health now limit you in going OUTSIDE the home, for example to shop or visit a doctor's office?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFA4	Does your health now limit you in doing heavy work around the house like scrubbing floors, or lifting or moving heavy furniture?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
		Without any difficulty	**With a little difficulty**	**With some difficulty**	**With much difficulty**	**Unable to do**
PFA12	Are you able to push open a heavy door?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFB28r1	Are you able to lift 10 pounds (5 kg) above your shoulder?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFA14r1	Are you able to carry a heavy object (over 10 pounds/5 kg)?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
		Not at all	**Very little**	**Somewhat**	**Quite a lot**	**Cannot do**
PFB1	Does your health now limit you in doing moderate work around the house like vacuuming, sweeping floors or carrying in groceries?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFA5	Does your health now limit you in lifting or carrying groceries?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1

		Without any difficulty	With a little difficulty	With some difficulty	With much difficulty	Unable to do
		Without any difficulty	**With a little difficulty**	**With some difficulty**	**With much difficulty**	**Unable to do**
PFA42	Are you able to carry a laundry basket up a flight of stairs?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFA13	Are you able to exercise for an hour?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1

16.3. EuroQol Five-Dimensional Descriptive System

Health Questionnaire

English version

Under each heading, please check the ONE box that best describes your health TODAY

MOBILITY

I have no problems walking ❑
I have slight problems walking ❑
I have moderate problems walking ❑
I have severe problems walking ❑
I am unable to walk ❑

SELF-CARE

I have no problems washing or dressing myself ❑
I have slight problems washing or dressing myself ❑
I have moderate problems washing or dressing myself ❑
I have severe problems washing or dressing myself ❑
I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(eg work, study, housework, family or leisure activities)*

I have no problems doing my usual activities ❑
I have slight problems doing my usual activities ❑
I have moderate problems doing my usual activities ❑
I have severe problems doing my usual activities ❑
I am unable to do my usual activities ❑

PAIN / DISCOMFORT

I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

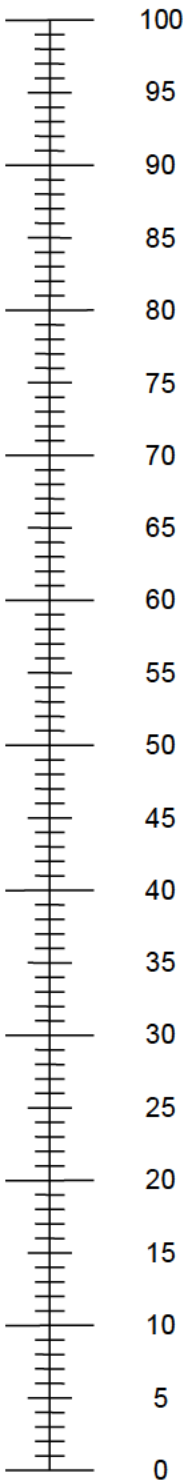
ANXIETY / DEPRESSION

I am not anxious or depressed ❑
I am slightly anxious or depressed ❑
I am moderately anxious or depressed ❑
I am severely anxious or depressed ❑
I am extremely anxious or depressed ❑

- We would like to know how good or bad your health is TODAY.

  - This scale is numbered from 0 to 100.
  - 100 means the best health you can imagine.
    0 means the worst health you can imagine.
  - Mark an X on the scale to indicate how your health is TODAY.
  - Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



16.4. Surgical Assessment Questionnaire

Table 16.1: Sample Surgical Assessment Questionnaire

Question	Response
Expected probability of a complete resection with no microscopic residual tumor:	High Medium Low None
Expected postoperative morbidity:	None Mild Moderate Severe
Complexity of surgical procedure:	Low Medium High
Operative risk due to other medical conditions:	Low Medium High Pre-Operative Assessment Not Done

16.5. Long Term Follow-up Questionnaire

Table 16.2: Sample Long Term Follow-up Questionnaire

Question	Response
Did TGCT worsen or recur after study treatment discontinuation?	• No • Yes A) Symptoms worse or recurred: Yes / No / Unknown B) Functional Impairment worse or recurred: Yes / No / Unknown C) Radiographic progression: Yes / No / Unknown • Other, describe (lost to follow-up, death, etc): _____
Was/were MRI performed >3 months after study treatment discontinuation?	• No • Unknown • Yes: Date of assessment: _____, Result: CR, PR, SD, PD, NE (repeating to enter each MRI until PD or other TGCT intervention)
Was there surgery for TGCT >3 months after study treatment discontinuation?	• No • Yes: Date of first surgery after discontinuation: _____, Reason for surgery: ___ Resection___ Other, describe: _____
Was systemic anti-tumor therapy for TGCT given after study treatment discontinuation?	• No • Yes: Date of first treatment: _____, Agent: _____
Was radiotherapy for TGCT given after study treatment discontinuation?	• No • Yes: Date of radiotherapy: _____

CR = complete response; PR = partial response; SD = stable disease; PD = progressive disease; NE = not evaluable.

16.6. Schedule of Assessment

Table 16.3: Schedule of Assessment

Schedule of Assessment (Completion of study at Week 25, day before C7D1)

Procedure	Day -42 to -1 [a]	C1D1	C1D8 ± 2d	C1D15 ± 2d	C1D22 ± 2d	C2D1 ± 2d	C2D8 ± 2d	C2D15 ± 2d	C2D22 ± 2d	C3D1 ± 7d	C3D15 ± 7d	C4D1 ± 7d	C5D1 ± 7d	C6D1 ± 7d	C7D1 [b] ± 7d	Post T [c] ± 7d	End St/Ear. Term. ± 7d	Long term follow-up ± 14d
	Screen [a]	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Week 7	Week 8	Week 9	Week 11	Week 13	Week 17	Week 21	Week 25	LD+28d	LD+12 Week / < new Tx [d]	Every 6 month after End St/Ear. Term
Informed consent	X																	
Demographics & medical history	X																	
Height, weight	X														X [e]	X [e]		
Vital signs, incl. BP, pulse rate, temperature [f]	X	X		X		X				X		X	X	X	X	X		
Physical examination [g]	X					X						X			X	X		
ECG [h]	X	X		X											X	X		
Chemistry, hematology	X	X		X [i]		X				X		X	X	X	X	X		
Liver tests [j]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Urinalysis		X										X			X	X		
Hepatitis panel	X																	
Coagulation tests [k]		X													X	X		
Hormone testing [l]	X	X													X	X		
PROMIS Physical Function Scale	X	X								X			X		X	X		
EQ-5D-5L	X	X								X			X		X	X		
MRI of the affected joint [m]	X											X			X	X	X	
Photographic documentation of tumor	X											X			X	X	X	

Procedure	Day -42 to -1 [a]	C1D1	C1D8 ± 2d	C1D15 ± 2d	C1D22 ± 2d	C2D1 ± 2d	C2D8 ± 2d	C2D15 ± 2d	C2D22 ± 2d	C3D1 ± 7d	C3D15 ± 7d	C4D1 ± 7d	C5D1 ± 7d	C6D1 ± 7d	C7D1 [b] ± 7d	Post T [c] ± 7d	End St/Ear. Term. ± 7d	Long term follow-up ± 14d
	Screen [a]	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Week 7	Week 8	Week 9	Week 11	Week 13	Week 17	Week 21	Week 25	LD+28d	LD+12 Week / < new Tx [d]	Every 6 month after End St/Ear. Term
Range of motion assessment [n]	X											X			X	X		
Serum pregnancy test	X[o]					X				X		X	X	X	X	X	X	
PK, PDy blood sampling[p]		X		X		X				X			X					
Surgical Assessment Questionnaire	X														X	X		
Analgesic use assessment	X[q]	X		X		X				X		X	X	X	X	X		
Dispense study Tx		X				X				X		X	X	X	X			
Study drug dosing at site[r]		X		X											X			
Tx compliance assessment				X		X				X		X	X	X	X			
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Adverse events [s]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Collection of surgical data [t]																X	X	
AMA[u]	X	X																
Subject status[v]																		X

AE = adverse event; ALT = alanine aminotransferase; AMA = Anti-mitochondrial antibody; AST = aspartate aminotransferase; BP = blood pressure; C = cycle; D/d = Day; ECG = electrocardiogram; End St./Ear. Term. = End-of-Study/Early Termination; FSH = follicle-stimulating hormone; GGT = gamma-glutamyl transferase; incl. = including; LD = last dose; MRI = magnetic resonance imaging; PDy = pharmacodynamic; PK = pharmacokinetic; PROMIS = Patient-reported Outcomes Measurement Information System; Pt = patient; TGCT = tenosynovial giant cell tumor; Tx = treatment.

a Procedures performed as part of patient care within the 42-day period before the first dose of study drug may be used for screening purposes if they conform to protocol requirements and standards. All screening test results must be reviewed prior to dosing to assess the study candidate's eligibility for inclusion.

b The Cycle 7, Day 1 visit (C7D1) applies to patients who are continuing or not continuing the study.

c Patients who exit the study with radiologic disease progression will undergo their last study evaluation 28 ± 7 days after their last dose of study drug and before any new TGCT therapy, including surgery, whichever occurs first. Any planned new TGCT therapy, including the type of surgical procedure, will be recorded. Patients who withdraw from the study with radiologic progression do not undergo an End of Study/Early Termination MRI.

d Patients who end their study participation with no radiologic disease progression will undergo post-treatment procedures 28 ± 7 days after their last dose of study drug and a final MRI 12 weeks ± 7 days after their last dose of study drug or before any new TGCT therapy, including surgery, whichever occurs first. The latter MRI need not be performed if new TGCT therapy starts within 4 weeks of the Post-treatment visit. Before or at the End-of-Study/Early Termination visit, plans for any new TGCT therapy will be obtained.

e Weight only.

f Vital signs should be performed before any invasive procedures are carried out on the same day.

g In the event of early withdrawal, a physical examination is performed at the Post-treatment visit.

h A standard 12-lead ECG is performed prior to dosing. Patients should be told not to take their morning dose of study drug at home on days when an ECG is performed; instead, they should bring their study drug bottle to the site and take their morning dose upon site instruction. At the C1D1 and C1D15 visits only, the ECG is performed before and 2 hours after dosing. The ECG before dosing should be performed before any invasive procedures are carried out on the same day. The 2 hour post-dose ECG should begin within ± 10 minutes of the 2 hour post-dose time point.

i Hematology only.

j Alkaline phosphatase, ALT, AST, total and direct bilirubin, and GGT should be assessed at Screening, weekly for the first 8 weeks (until C3D1) and every 2 weeks for the next month (C3D15 and C4D1), then every month thereafter.

k Patients receiving concomitant warfarin should have their anti-coagulation status carefully monitored for any necessary dose adjustments (see Section 5.6).

l Women who are not using hormonal contraception must be tested for levels of FSH, LH, progesterone, and estradiol. Hormone testing will not be required for women who have either had an oophorectomy or are post-menopausal. Men must be tested for levels of LH, FSH, and testosterone. Men whose testosterone level is below baseline at the last study visit must be followed until their level has stabilized or returned to baseline.

m MRI of the affected joint should be performed within 56 days prior to C1D1. The Investigator may request a centrally read blinded MRI to confirm progression, eg, if a subject's mid-study clinical profile or local radiologic assessment indicates progression.

n A range of motion assessment in the affected joint will be performed by a qualified assessor.

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

p Details on blood sampling are found in Table 8.1 (PK) and Section 8.1 (PDy).

q A diary of analgesic use must be kept for the 7-day period before the first dose of study drug.

r The morning dose of study drug should be administered at the site on the days indicated.

s After the patient provides signed informed consent; AEs are monitored throughout the study via safety assessments, observation, and patient reporting (see Section 9.5).

t If surgical resection of the tumor is performed within the designated time period (28 days for Post-Tx and 12 weeks for End St/Ear Term) after the last dose of study drug, details of the surgery and its outcome should be obtained.

u Serum sample should be collected for AMA at screening and once severe hepatotoxicity is observed (Section 5.4).

v Subject status will be collected by telephone contact every 6 months from each subject who consent.

Schedule of Assessment (Study drug continuation after Week 25)

Procedure	C10+D1 ± 7d[a]	Post Tx ± 7[b]	End St/Ear. Term. ± 7d	Long term follow-up ± 14d
	Week 37+	LD+28d	LD+12 Week / < new Tx [c]	Every 6 month after End St/Ear. Term
Weight		X		
Vital signs, incl. BP, pulse rate, temperature[d]	X	X		
Physical examination[e]	X	X		
ECG[f]		X		
Chemistry, hematology	X	X		
Liver tests[g]	X	X		
Urinalysis		X		
Coagulation tests[h]		X		
Hormone testing[i]		X		
PROMIS Physical Function Scale	X	X		
EQ-5D-5L	X	X		
MRI of the affected joint[j]	X	X	X	
Photographic documentation of tumor	X	X	X	
Range of motion assessment[k]	X	X		
Serum pregnancy test	X	X	X	
Surgical Assessment Questionnaire		X		
Analgesic use assessment	X	X		
Dispense study Tx	X			
Tx compliance assessment	X			
Concomitant medications	X	X	X	
Adverse events	X	X	X	
Collection of surgical data[l]		X	X	
AMA[m]	X			
Subject status[n]				X

AE = adverse event; ALT = alanine aminotransferase; AMA = Anti-mitochondrial antibody; AST = aspartate aminotransferase; BP = blood pressure; C = cycle; D/d = Day; ECG = electrocardiogram; End St./Ear. Term. = End-of-Study/Early Termination; FSH = follicle-stimulating hormone; incl. = including; LD = last dose; MRI = magnetic resonance imaging; PROMIS = Patient-reported Outcomes Measurement Information System; Pt = patient; TCGT = tenosynovial giant cell tumor; Tx = treatment.

a The procedures are performed at C10+D1 and every 12 weeks thereafter (eg, C13, C16, C19).

b Patients who exit the study with radiological disease progression will undergo their last study evaluation 28 ± 7 days after their last dose of study drug and before any new TGCT therapy, including surgery, whichever occurs first. Any planned new TGCT therapy, including the type of surgical procedure, will be recorded. Patients who withdraw from the study with radiological progression do not undergo an End of Study/Early Termination MRI.

c Patients who end their study participation with no radiological disease progression will undergo post-treatment procedures 28 ± 7 days after their last dose of study drug and a final MRI 12 weeks ± 7 days after their last dose of study drug or before any new TGCT therapy, including surgery, whichever occurs first. The latter MRI need not be performed if new TGCT therapy starts within 4 weeks of the Post-treatment visit. Before or at the End-of-Study/Early Termination visit, plans for any new TGCT therapy will be obtained.

d Vital signs should be performed before any invasive procedures are carried out on the same day.

e In the event of early withdrawal, a physical examination is performed at the Post-treatment visit.

f A standard 12-lead ECG is performed prior to dosing. Patients should be told not to take their morning dose of study drug at home on days when an ECG is performed; instead, they should bring their study drug bottle to the site and take their morning dose upon site instruction.

g Alkaline phosphatase, ALT, AST, total and direct bilirubin, and GGT should be assessed on Day 1 of every 3 cycles thereafter.

h Patients receiving concomitant warfarin should have their anti-coagulation status carefully monitored for any necessary dose adjustments (see Section 5.6).

i Women who are not using hormonal contraception must be tested for levels of FSH, LH, progesterone, and estradiol. Hormone testing will not be required for women who have either had an oophorectomy or are post-menopausal.

j The Investigator may request a centrally read blinded MRI to confirm progression, eg, if asubject's mid-study clinical profile or local radiologic assessment indicates progression.

k A range of motion assessment in the affected joint will be performed by a qualified assessor.

l If surgical resection of the tumor is performed within the designated time period (28 days for Post-Tx and 12 weeks for End St/Ear Term) after the last dose of study drug, details of the surgery and its outcome should be obtained.

m Serum sample should be collected for AMA once severe hepatotoxicity is observed (Section 5.4).

n Subject status will be collected by telephone contact every 6 months from each subject who consent.