CLINICAL STUDY PROTOCOL

A PHASE 2, MULTICENTER, TWO-PART, OPEN-LABEL STUDY OF PEXIDARTINIB IN ADULT SUBJECTS WITH TENOSYNOVIAL GIANT CELL TUMOR IN JAPAN

PROTOCOL NUMBER: PL3397-A-J304

VERSION 4.0, 27 Aug 2024

DAIICHI SANKYO, CO. LTD

3-5-1, Nihonbashi-honcho, Chuo-ku

Tokyo, 103-8426, Japan

INVESTIGATOR AGREEMENT

A PHASE 2, MULTICENTER, TWO-PART, OPEN-LABEL STUDY OF PEXIDARTINIB IN ADULT SUBJECTS WITH TENOSYNOVIAL GIANT CELL TUMOR IN JAPAN

Sponsor Approval:

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

PPD	
Print Name	**Signature**
PPD Clinical Science Department	
Title	**Date (DD MMM YYYY)**

Investigator's Signature:

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

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

I agree to conduct this study according to this protocol and to comply with its requirements, subject to ethical and safety considerations and guidelines, and to conduct the study in accordance with International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Guideline for Good Clinical Practice (ICH E6[R2]), which has its foundations in the Declaration of Helsinki, 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)**

DOCUMENT HISTORY

Version Number	Version Date
4.0	27 Aug 2024
3.0	10 Feb 2021
2.0	07 Oct 2020
1.0	08 Sep 2020

SUMMARY OF CHANGES

Please refer to the comparison document for protocol Version 3.0 (dated 10 Feb 2021) vs. protocol Version 4.0 (dated 27 Aug 2024) for actual changes in text. The summary of changes below is a top-line summary of major changes in the current PL3397-A-J304 clinical study protocol (Version 4.0) by section.

Amendment Rationale:

This protocol amendment is due to the Sponsor's decision to halting enrollment of new participants and not proceed with Part 2. Depending on this decision, the end of study duration and the assessment schedule will be changed.

Section # and Title	Description of Change	Brief Rationale
1.1. Protocol Synopsis	Study Design In June 2024, the sponsor decided to halt the enrollment of participants after 9 subjects were enrolled in Part 1 and not proceed with Part 2. The safety, PK, and efficacy in Part 2 will not be assessed. Study Duration Enrollment was planned to occur over approximately 17 months for Part 1 and Part 2, with treatment and follow-up projected to continue for approximately 27 months after the last subject was enrolled in Part 2. Anticipated total duration of the study was planned to be approximately 44 months. In June 2024, the sponsor decided to halt the enrollment of participants after 9 subjects were enrolled in Part 1. For the subjects receiving the study drug in Part 1 and wish to continue receiving it from Protocol Version 4.0 onwards, the study drug administration will be allowed to continue until February 2026. The study will continue until the overall EOS is reached.	Due to changes in development plans.
1.2. Study Schema	In June 2024, the sponsor decided to halt the enrollment of participants after 9 subjects were enrolled in Part 1 and not proceed with Part 2.	Due to changes in development plans.
1.3. Schedule of Assessments Table 1.1 Table 1.3	Table 1.1 and Table 1.3 (Added asterisks for each assessment item below.) Biomarker blood sample, Tumor biopsy sample, Range of motion, PROMIS Physical Function Scale, BPI Worst Pain NRS, EQ-5D-5L, Surgical Assessment Questionnaire, Analgesic use assessment, Photographic documentation of tumor, Log-term follow-up questionnaire (Added a double asterisk for an assessment item below.) MRI of the affected joint	In order to reduce the burden on subjects, non-essential efficacy assessment items will be reduced or halted in Part 1.

Section # and Title	Description of Change	Brief Rationale
	Footnote *: Not be performed from Protocol Version 4.0 onwards. **: From Protocol Version 4.0 onwards, only local review will be performed, and central review will not be performed. Table 1.3 (Added a triple asterisk for an assessment item below.) MRI of the affected joint Footnote ***: MRI are performed every 24 weeks from Protocol Version 4.0 onwards.	
3. OBJECTIVES, OUTCOME MEASURES, AND ENDPOINTS Table 3.1	Exploratory Objectives Part 1: To evaluate the efficacy of pexidartinib Outcome Measure, Endpoints The outcome measures planned for assessing the efficacy of the primary objectives, the secondary objectives, and the exploratory objectives Category Efficacy	Due to changes in development plans.
4.1.1. Design Overview	In June 2024, the sponsor decided to halt the enrollment of participants after 9 subjects were enrolled in Part 1 and not proceed with Part 2.	Due to changes in development plans.
4.1.4. Duration Overall Study Duration	Enrollment was planned to occur over approximately 17 months for Part 1 and Part 2, with treatment and follow-up projected to continue for approximately 27 months after the last subject was enrolled in Part 2. Anticipated total duration of the study was planned to be approximately 44 months. In June 2024, the sponsor decided to halt the enrollment of participants after 9 subjects were enrolled in Part 1. For the subjects receiving the study drug in Part 1 and wish to continue receiving it from Protocol Version 4.0 onwards, the study drug administration will be allowed to continue until February 2026.	Due to changes in development plans.
6.7. Prior and Concomitant Medications Prohibited Therapies/Products	Joint aspiration* *: Not to be prohibited from Protocol Version 4.0 onwards.	In order to reduce the burden on subjects.
7.1. Discontinuation of Study Drug	During the study, if a subject experiences radiological progression documented by central or local 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 Medical Monitor or designee to allow the subject to remain in the study.	Due to completion of tumor assessment by central review.

Section # and Title	Description of Change	Brief Rationale
8.3. Efficacy Assessments Tumor Imaging	All MRI scans up to Protocol Version 3.0 will be centrally read, while MRI scans from Protocol Version 4.0 onwards will not be centrally read. Local evaluation of radiological response, 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 up to Protocol Version 3.0 will be read centrally. 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. While progression status will be assessed only by local read from Protocol Version 4.0 onwards. The details for MRI scan read are outlined in the MRI Procedure Manual.	Non-essential efficacy assessment items including the central MRI assessment will be reduced or halted in Part 1.
8.6.1. Biomarker Analysis for Pharmacodynamics	(Added an asterisk for a section title) *: Sample collection will not be performed from Protocol Version 4.0 onwards.	Due to reducing the burden on subjects.
8.6.2. Biomarker Analysis for Subject Characterization	(Added an asterisk for a section title) *: Sample collection will not be performed from Protocol Version 4.0 onwards.	Due to reducing the burden on subjects.
9.1. General Statistical Considerations	For all analysis, the Part 1 data at the end of Part 1 will be used. The all analysis including the efficacy analysis of the subjects in Part 1 was originally planned to be performed at the end of Part 2. However, the sponsor decided not to proceed with Part 2. Depending on this decision, the Part 1 data will be analyzed at the end of Part 1, and the efficacy analysis will be performed as the exploratory analysis.	Due to changes in development plans.
9.2. Statistical Hypothesis	In June 2024, the sponsor decided not to proceed with Part 2. Therefore, the statistical hypothesis for Part 2 will not be confirmed.	Due to changes in development plans.
9.5.1. Efficacy Analyses	In June 2024, the sponsor decided not to proceed with Part 2. Therefore, the primary efficacy analysis and the secondary efficacy analysis will be performed as the exploratory efficacy analysis using Part 1 data.	Due to changes in development plans.

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1. PROTOCOL SUMMARY

1.1. Protocol Synopsis

Protocol Title
A Phase 2, Multicenter, Two-Part, Open-Label Study of Pexidartinib in Adult Subjects with Tenosynovial Giant Cell Tumor in Japan
Protocol Short Title
Japan Ph2 Study of Pexidartinib in TGCT
Protocol Number
PL3397-A-J304
Sponsor/Collaborators
Daiichi Sankyo, Co., Ltd.
Registry Identification(s)
IND Number
Not applicable
Study Phase
Phase 2
Planned Geographical Coverage, Study Sites and Location
Japan
Study Population
Symptomatic tenosynovial giant cell tumor (TGCT), also known as pigmented villonodular synovitis (PVNS) and giant cell tumor of the tendon sheath (GCT TS), associated with severe morbidity or functional limitations and not amenable to improvement with surgery.
Study Objectives/Outcome Measures and Endpoints

The table below lists primary and secondary study objectives and endpoints which have outcome measures.

Objectives	Outcome Measure	Endpoints	Category
Primary			
Part 1: To evaluate the tolerability and pharmacokinetics (PK) of pexidartinib in Japanese subjects	**Title:** Dose-limiting toxicity (DLT) **Description:** Number of subjects with DLTs **Time frame:** Cycle 1 Day 1 (C1D1) to C1D28	Number of subjects with DLTs	Safety
	Title: PK profile **Description:** Plasma concentrations and PK parameters of pexidartinib and	Plasma concentrations and PK parameters of pexidartinib and ZAAD-1006a, the major metabolite of pexidartinib	PK

	ZAAD-1006a, the major metabolite of pexidartinib **Time frame:** C1D1-C1D2 and C1D15 (with intensive sampling)		
Part 2: To evaluate the efficacy of pexidartinib in Japanese subjects	**Title:** Objective response rate (ORR) based on Response Evaluation Criteria in Solid Tumors, version 1.1 (RECIST 1.1) **Description:** ORR as assessed by centrally reviewed magnetic resonance imaging (MRI) scan based on RECIST 1.1. **Time frame:** Week 25	ORR is defined as the proportion of subjects who achieved a complete response (CR) or partial response (PR) based on RECIST 1.1 by centrally reviewed MRI scan. No confirmation (ie, CR or PR at the subsequent MRI assessment) will be required for a CR or PR.	Efficacy
Secondary			
Part 2: To evaluate the efficacy of pexidartinib	**Title:** ORR based on tumor volume score (TVS) **Description:** ORR as assessed by centrally reviewed MRI scan based on TVS **Time frame:** Week 25	ORR is defined as the proportion of subjects who achieved a CR or PR based on TVS by centrally reviewed MRI scan	Efficacy
	Title: Range of motion (ROM) **Description:** Raw measurements of the affected joint with a goniometer **Time frame:** Week 25	Mean change from baseline in ROM of the affected joint, relative to a reference standard for the same joint	Efficacy
	Title: Patient-Reported Outcomes Measurement Information System (PROMIS) Physical Function Scale **Description:** Patient-Reported Outcomes (PRO) relevant to the assessment of lower and upper limb function **Time frame:** Week 25	Mean change from baseline score in the PROMIS Physical Function Scale	Efficacy
	Title: Brief Pain Inventory (BPI) Worst Pain Numeric Rating Scale (NRS) **Description:** PRO relevant to the assessment of the "worst" pain in the last 24 hours **Time frame:** Week 25	Proportion of responders based on the BPI Worst Pain NRS item and analgesic use by BPI-30 definition (ie, 30% or more improvement in average NRS)	Efficacy
	Title: Best overall response (BOR) based on RECIST 1.1	BOR is defined as the proportion of subjects who achieved CR, PR, stable disease (SD), progressive	Efficacy

	Description: BOR as assessed by centrally reviewed MRI scan based on RECIST 1.1 **Time frame:** At the time of the primary analysis: After all subjects have made the Week 25 visit or have discontinued from the study, whichever occurs first	disease (PD), and not evaluable (NE) recorded as the best response based on RECIST 1.1 by centrally reviewed MRI scan	
	Title: BOR based on TVS **Description:** BOR as assessed by centrally reviewed MRI scan based on TVS **Time frame:** At the time of the primary analysis	BOR is defined as the proportion of subjects who achieved CR, PR, SD, PD, and NE recorded as the best response based on TVS by centrally reviewed MRI scan	Efficacy
	Title: Duration of response (DoR) based on RECIST 1.1 **Description:** DoR as assessed by centrally reviewed MRI scan based on RECIST 1.1 **Time frame:** At the time of the primary analysis	DoR is defined as the time from the date of the first recorded response to the first date of documented disease progression	Efficacy
	Title: DoR based on TVS **Description:** DoR as assessed by centrally reviewed MRI scan based on TVS **Time frame:** At the time of the primary analysis	DoR is defined as the time from the date of the first recorded response to the first date of documented disease progression	Efficacy
Part 1, Part 2: To assess the safety of pexidartinib	**Title:** Treatment-emergent adverse events (TEAEs) and other safety parameters during the study* **Description:** Descriptive statistics of safety endpoints **Time frame:** Continuous monitoring and reported at the time of each data cut-off *Though this is a secondary objective, this is a primary outcome measure	Safety evaluation include the following, but is not limited to: TEAEs, drug induced hepatotoxicity, laboratory tests, vital signs, and electrocardiogram (ECG)	Safety
Part 1, Part 2: To evaluate the PK properties of pexidartinib	**Title:** PK profile **Description:** Plasma concentrations and PK parameters of pexidartinib and ZAAD-1006a **Time frame:** Part 1; C2D1, C3D1, and C5D1 (with sparse sampling), Part 2; C1D1-C1D2 and C1D15 (with intensive	Plasma concentrations and PK parameters of pexidartinib and ZAAD-1006a, the major metabolite of pexidartinib	PK

	sampling) and C2D1, C3D1, C5D1 (with sparse sampling)			

Study Design

This is a phase 2, multicenter, two-part, open-label, single-arm study, conducted in Japan, which is aimed to evaluate the safety, tolerability, PK, and efficacy of pexidartinib in adult subjects with symptomatic TGCT associated with severe morbidity or functional limitation and not amenable to improvement with surgery. This study consists of 2 parts: In Part 1, the tolerability and PK of pexidartinib 800 mg/day (400 mg twice a day [BID]) given on an empty stomach will be evaluated to determine the initiation of Part 2, and in Part 2, the efficacy, safety, and PK of pexidartinib 800 mg/day (400 mg BID) given on an empty stomach will be evaluated.

Part 1:

Pexidartinib will be administered at 400 mg once (2 capsules in the morning) on C1D1 to evaluate the PK profile for 24 hours. From C1D2 and after, pexidartinib will be administered at 400 mg BID (2 capsules in the morning and 2 capsules in the evening). Pexidartinib must be administered on an empty stomach (at least 1 hour before or 2 hours after a meal or snack).

Evaluation of tolerability is based on review of all DLT-evaluable subjects who have received pexidartinib and have either completed the minimum safety evaluation requirements over the DLT evaluation period (28 days) or have experienced a DLT during the DLT evaluation period. If a DLT is observed in 1 of 3 subjects, at least 6 subjects in total will be treated in Part 1. If a DLT is observed in 0 of 3 subjects or 1 of 6 subjects in Part 1, Part 2 will be initiated. If a DLT is observed in ≥2 of 3 subjects or ≥2 of 6 subjects in Part 1, the safety monitoring committee will discuss whether more subjects should be added to Part 1. Transition to Part 2 will be considered based on review of the tolerability, available safety and PK data from Part 1.

Pexidartinib will be administered continuously with a 28-day treatment cycle until the criteria for discontinuation are reached. The subjects who complete 24 weeks of dosing and 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. The safety, tolerability, PK, and efficacy will be assessed during the study according to the schedule of assessments.

Part 2:

Pexidartinib will be administered at 400 mg once (2 capsules in the morning) on C1D1 to evaluate the PK profile for 24 hours. From C1D2 and after, pexidartinib will be administered at 400 mg BID (2 capsules in the morning and 2 capsules in the evening). Pexidartinib must be administered on an empty stomach (at least 1 hour before or 2 hours after a meal or snack).

Pexidartinib will be administered continuously with a 28-day treatment cycle until the criteria for discontinuation are reached. The subjects who complete 24 weeks of dosing and 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. The safety, PK, and efficacy will be assessed during the study according to the schedule of assessments.

In June 2024, the sponsor decided to halt the enrollment of participants after 9 subjects were enrolled in Part 1 and not proceed with Part 2. The safety, PK, and efficacy in Part 2 will not be assessed.

The **primary completion date** is the date when all enrolled subjects have completed the predetermined duration of treatment (ie, the date when all DLT-evaluable subjects have either completed minimum safety evaluation requirements over the DLT evaluation period [28 days] or have experienced a DLT during the DLT evaluation period for Part 1, Week 25 for Part 2) or have discontinued the study. This date is used as the cut-off date for the analysis of the primary endpoint of the study. All subjects still on treatment and continuing to derive benefit from study drug at the Primary Completion Date will continue to follow the study schedule of assessments until the **overall End of Study (EOS)** is reached.

Overall EOS will occur when:

- the last subject last visit has occurred

- all subjects have discontinued treatment or discontinued the study or have died
- an alternative study becomes available for subjects continuing to derive benefit from treatment with pexidartinib, where the study drug is offered to these subjects
- the study is discontinued by the Sponsor for other reasons (administrative, program-level, or class-related)

The subject's EOS is the date of their last study visit/contact.

Study Duration

The study start date is the date when the first subject has signed informed consent. A subject is eligible to be enrolled into the interventional phase of the study when the Investigator or designee has determined that all inclusion and exclusion criteria have been satisfied, including having obtained written informed consent.

Enrollment was planned to occur over approximately 17 months for Part 1 and Part 2, with treatment and follow-up projected to continue for approximately 27 months after the last subject was enrolled in Part 2.

Anticipated total duration of the study was planned to be approximately 44 months.

In June 2024, the sponsor decided to halt the enrollment of participants after 9 subjects were enrolled in Part 1. For the subjects receiving the study drug in Part 1 and wish to continue receiving it from Protocol Version 4.0 onwards, the study drug administration will be allowed to continue until February 2026.

The study will continue until the overall EOS is reached.

Key Eligibility Criteria

Key Inclusion Criteria:

Subjects eligible for inclusion in this study have to meet all inclusion criteria for this study. Below is a list limited to the key inclusion criteria:

- Age ≥20 years
- A diagnosis of TGCT (i) that has been histologically confirmed by a pathologist[1] 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).
- 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.
- Stable prescription of analgesic regimen during the 2 weeks prior to enrollment.
- Adequate hematologic, hepatic, and renal function, defined by:
  - Absolute neutrophil count ≥1.5 × 10^9/L
  - Hemoglobin >10 g/dL
  - Platelet count ≥100 × 10^9/L
  - Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤1.0 ×upper limit of normal (ULN)
  - Total bilirubin and direct bilirubin ≤1.0 × ULN
  - Alkaline phosphatase (ALP) ≤1.0 × ULN

  - Creatinine clearance (CL_{CR}) >15 mL/min

- If the subject is a female of childbearing potential, she must have a negative serum pregnancy test within 14 days before enrollment and must be willing to use highly effective birth control with a non-hormonal method of contraception upon enrollment, during the Treatment Period, and for 1 month following the last dose of study drug. A female is considered of childbearing potential following menarche and until becoming postmenopausal (no menstrual period for a minimum of 12 months and a follicle-stimulating hormone [FSH] level >40 mIU/mL) unless permanently sterile (undergone a hysterectomy, bilateral salpingectomy or bilateral oophorectomy).
- If male, the subject must be surgically sterile or willing to use highly effective birth control upon enrollment, during the treatment period, and for 1 month following the last dose of study drug.
- Male subjects must not freeze or donate sperm starting at Screening and throughout the study period, and at least 1 month after the final study drug administration.
- Female subjects must not donate, or retrieve for their own use, ova from the time of screening and throughout the study treatment period, and for at least 1 month after the final study drug administration.
- Willingness and ability to undergo tumor biopsy at screening or willingness to provide archived tissue samples for assessment of biomarkers

Key Exclusion Criteria:

Subjects meeting any exclusion criteria for this study will be excluded from this study. Below is a list limited to the key exclusion criteria:

- Inadequate washout period before enrollment, defined as:
  - Investigational drug/device use within <28 days
- Previous use of pexidartinib or any selective treatment targeting colony stimulating factor 1 (CSF-1) or the colony-stimulating factor 1 receptor (CSF1R); previous use of oral multi-kinase inhibitors (eg, imatinib or nilotinib) are allowed.
- Active cancer, except for the tumor for which the subject is enrolled in the study, (either concurrent or within the last year of starting the 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.
- Known metastatic TGCT.
- Active, chronic, inactive carrier, or resolved infection hepatitis C or hepatitis B infection, except for patients only positive for HBs antibody (HBs antigen negative and HBc antibody negative) and with clear prior vaccination. Or known active or chronic infection with the human immunodeficiency virus.
- Pre-existing increased serum transaminases; total bilirubin or direct bilirubin (>ULN); or active liver or biliary tract disease, including increased ALP.

- Known active tuberculosis.
- 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.
- Use of strong cytochrome P450 (CYP) 3A inducers, including St John's wort, proton pump inhibitors (PPIs) and potassium-competitive acid blockers (P-CABs), or other products known to cause hepatotoxicity.

Investigational Medicinal Product, Dose and Mode of Administration

The study drug, pexidartinib, will be administered orally daily in capsule form. Each capsule will contain 200 mg of pexidartinib (J-3397-AF in hydroxypropyl methylcellulose capsules). Pexidartinib will be administered at 400 mg once (2 capsules in the morning) on C1D1 to evaluate the PK profile for 24 hours. From C1D2 and after, pexidartinib will be administered at 400 mg BID (2 capsules in the morning and 2 capsules in the evening). Pexidartinib must be administered on an empty stomach (at least 1 hour before or 2 hours after a meal or snack), at approximately the same times of the day, and approximately 12 hours apart.

Active Ingredient(s)/INN

pexidartinib (PLX3397):

5-[(5-Chloro-1*H*-pyrrolo[2,3-*b*]pyridine-3-yl)methyl]-*N*-{[6-(trifluoromethyl)pyridine-3-yl]methyl}pyridine-2-amine monohydrochloride

Planned Sample Size

In Part 1:

Sample size was determined by practical considerations and no formal statistical assessment has been performed. The total sample size is 3 to 6 DLT evaluated subjects.

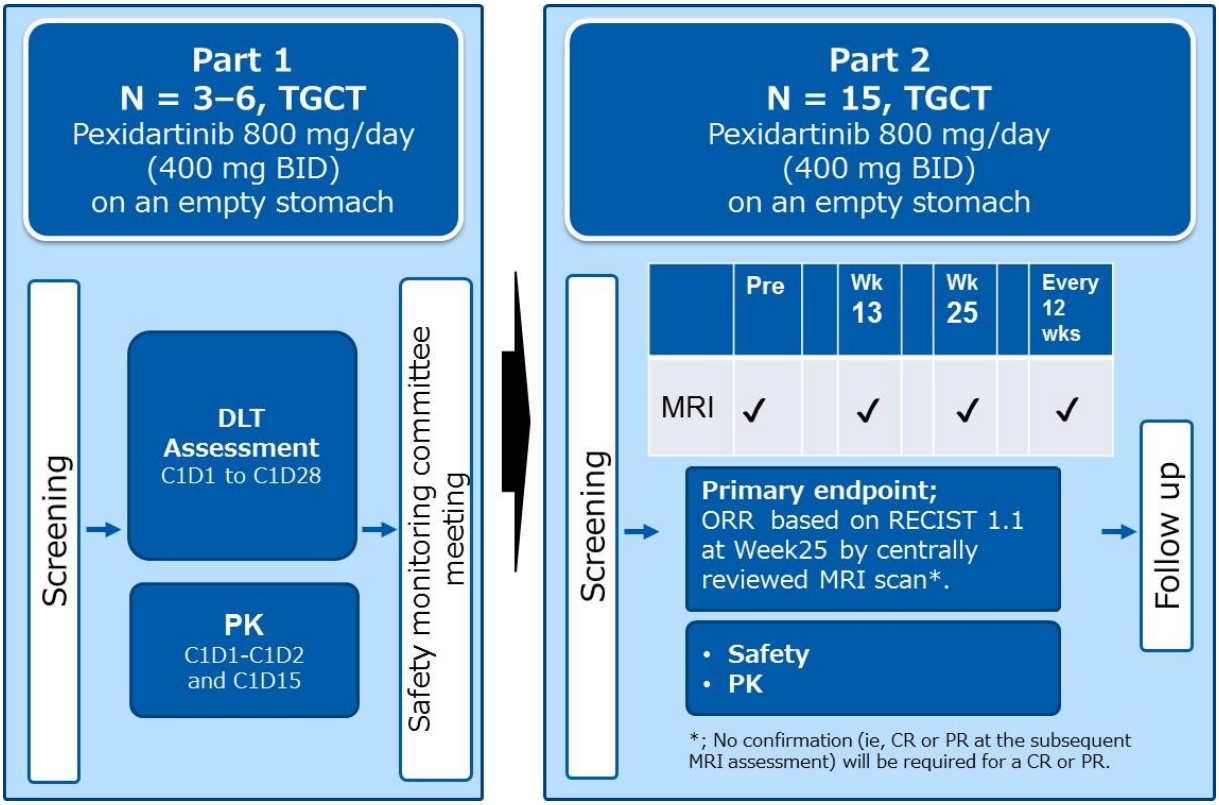
In Part 2:

15 subjects

The assumed responder rate for the primary endpoint is 37.7% from ORR for pexidartinib in the ENLIVEN study. Based on the use of a one-sided, exact binomial test of a proportion against the null hypothesis of 5% at the one-sided alpha = 0.05 level of significance, a sample size of 13 subjects provides more than 90% power to detect this magnitude of difference.

1.2. Study Schema

Figure 1.1: Study Level Flow Diagram



BID = twice a day; C = cycle; CR = complete response; D = day; DLT = dose-limiting toxicity; MRI = magnetic resonance imaging; PK = pharmacokinetics; PR = partial response; ORR = objective response rate; TGCT = tenosynovial giant cell tumor; RECIST = response evaluation criteria in solid tumors; Wk = week

In June 2024, the sponsor decided to halt the enrollment of participants after 9 subjects were enrolled in Part 1 and not proceed with Part 2.

1.3. Schedule of Assessments

Table 1.1: Schedule of Assessments (Part 1: from the Screening Period to Cycle 7 Day 1)

		SCR	C1					C2				C3		C4	C5	C6	C7[b]	Post Treat.[c]	End St/Ear.Term.[d]	LTFU[e]
	Day	-28[a] to -1	1	2	8	15	22	1	8	15	22	1	15	1	1	1	1			
	Week		1		2	3	4	5	6	7	8	9	11	13	17	21	25			
	Window				±2d	±2d	±2d	±2d	±2d	±2d	±2d	±7d	±7d	±7d	±7d	±7d	±7d	±7d	±7d	±14d
Informed consent		X																		
Eligibility Assessment		X[f]																		
Demographics & medical history		X																		
Vitals	Vital signs[g]	X[h]	X[i]	X	X	X	X	X		X		X		X	X	X	X	X		
	Height, weight	X															X[j]	X[j]		
Safety	Physical examination[k]	X[h]	X[i]	X	X	X	X	X		X		X		X			X	X		
	12-lead ECG[l]	X[h]	X[m]			X		X				X		X	X		X	X		
	ECHO/MUGA	X[n]						X							X					
Laboratory Assessments	Hematology, Chemistry	X[h]	X[m]	X	X	X	X	X		X		X		X	X	X	X	X		
	Liver tests	X[h]	X[m]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
	Coagulation tests[o]	X[h]	X[m]														X	X		
	Hepatitis panel	X																		
	Hormone testing[p]	X[h]	X[m]														X	X		
	Serum pregnancy test	X[q]						X				X		X	X	X	X	X	X	
	Urinalysis	X[h]	X[m]	X	X	X	X	X		X		X		X			X	X		
	SARS-CoV-2 Sample		X[i]											X			X	X		
	PK sample[r]		X	X		X		X				X			X					
	PK Sampling for CQ/HCQ Administration		If CQ or HCQ is administered for SARS-CoV-2, additional PK blood samples should be collected at the following visits: · Prior to the first CQ or HCQ dose (Day 1) · Day 3 or Day 4 of CQ or HCQ treatment, prior to CQ or HCQ dose (within 4h) · Last day of the CQ/HCQ treatment, prior to CQ/HCQ dose (within 4h) · The day of pexidartinib resumption, after the CQ/HCQ washout period[s], (within 8h BI of pexidartinib).																	
	Biomarker Blood Sample		X[i]			X		X				X			X			X*	X*	

		SCR	C1					C2				C3		C4	C5	C6	C7[b]	Post Treat.[c]	End St/Ear.Term.[d]	LTFU[e]
	Day	-28[a] to -1	1	2	8	15	22	1	8	15	22	1	15	1	1	1	1			
	Week		1		2	3	4	5	6	7	8	9	11	13	17	21	25			
	Window				±2d	±2d	±2d	±2d	±2d	±2d	±2d	±7d	±7d	±7d	±7d	±7d	±7d	±7d	±7d	±14d
	PGx Blood Sample		X[i]																	
	Tumor Biopsy sample	X[t]						X[u]										X[u,*]	X[u,*]	
	AMA[v]	X	X																	
Treatment Response/ Disease Assessment	MRI of the affected joint[w]	X												X			X	X**	X**	
	Range of motion assessment	X												X			X	X*		
	PROMIS Physical Function Scale[x]	X	X[i]									X			X		X	X*		
	BPI Worst Pain NRS[x,y]	X	X[i]									X			X		X	X*		
	EQ-5D-5L[x]	X	X[i]									X			X		X	X*		
	Surgical Assessment Questionnaire	X															X	X*		
	Analgesic use assessment[z]	X	X			X		X				X		X	X	X	X	X*		
	Photographic documentation of tumor	X												X			X	X*	X*	
Study Drug	Dispense study Tx		X		X	X	X	X	X	X	X	X	X	X	X	X	X			
	Study drug dosing at site[aa]		X			X		X				X		X	X		X			
	Tx compliance assessment				X	X	X	X	X	X	X	X	X	X	X	X	X			
Hospitalization			X																	
Concomitant medications		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Adverse events[bb]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Collection of surgical data[cc]																		X	X	
Long-term follow-up questionnaire																				X*

AE = adverse event; ALT = alanine aminotransferase; AMA = Anti-mitochondrial antibody; AST = aspartate aminotransferase; BPI = brief pain inventory; C = cycle; D/d = Day; CQ = chloroquine; ECG = electrocardiogram; End St./Ear. Term. = end of study/early termination; EQ-5D-5L = The five-level version of EuroQol five-dimensional questionnaire; FSH = follicle-stimulating hormone; HCQ = hydroxychloroquine; incl. = including; LTFU = long-term follow-up; MRI = magnetic resonance imaging; MUGA = multigated acquisition; NRS = numeric rating scale; Pdy = pharmacodynamic(s); PGx = pharmacogenomic(s); PK = pharmacokinetic(s); PROMIS = patient-reported outcomes measurement information system; Pt = patient; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; SCR = screening; TGCT = tenosynovial giant cell tumor; Tx = treatment.

a. Procedures performed as part of patient care within the 28-day period before the first dose of the 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 C7D1 applies to patients who are continuing and those who are not continuing the study.
c. 28 days after the last study drug administration. Patients who exit the study with radiologic disease progression will undergo their last study evaluation at 28 ± 7 days after their last dose of the 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. Last dosing +12 weeks or before new treatment. Patients who end their study participation with no radiologic disease progression will undergo post-treatment procedures at 28 ± 7 days after their last dose of the study drug and a final MRI at 12 weeks ± 7 days after their last dose of the 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. Every 6 months after the End of Study/Early Termination.
f. Time frame between enrollment and the first dose of the study drug can be up to 3 days prior to C1D1.
g. Vital signs including blood pressure, pulse rate, and temperature should be performed before any invasive procedures are carried out on the same day.
h. Within 7 days before the enrollment.
i. Before the first dose of the study drug.
j. Weight only.
k. In the event of early withdrawal, a physical examination is performed at the Post-treatment visit.
l. A standard 12-lead ECG is performed prior to dosing. Patients should be told not to take their morning dose of the 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 instruction at the site. 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.
m. Within 72 hours before the first dose of the study drug.
n. Within 21 days before the first dose of the study drug.
o. Patients receiving concomitant warfarin should have their anti-coagulation status carefully monitored for any necessary dose adjustments.
p. Women who are not using hormonal contraception must be tested for levels of FSH, luteinizing hormone (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.

q. Women of childbearing potential must have a serum pregnancy test within 14 days before enrollment.
r. Details on blood sampling are found in Section 8.5.
s. A washout period of no less than 14 days is required before restarting pexidartinib.
t. Must be collected during screening. A tumor biopsy that was recently collected may be substituted for the biopsy collected during screening. Screening biopsy should only be collected after all other eligibility criteria are met (an archived tissue sample may be acceptable upon sponsor's/designee approval). A screening biopsy should only be collected after all other eligibility criteria are met.
u. Optional.
v. A serum sample should be collected for AMA at screening and when severe hepatotoxicity is observed.
w. MRI of the affected joint should be performed within 56 days before the first dose of the study drug.
x. Before any invasive procedures on the same day, PROMIS Physical Function Scale, BPI Worst Pain NRS, and EQ-5D-5L are to be recorded. PROMIS Physical Function Scale will be assessed on patients who signed informed consent after the Japanese translated version of PROMIS Physical Function Scale is ready.
y. Subjects will complete the BPI Worst Pain NRS item for seven consecutive days prior to C1D1, C3D1, C5D1, C7D1 and Post-Tx, as well as on the day of the study visit. In addition, subjects will complete the BPI Worst Pain NRS item on an outpatient basis prior to the indicated study visits.
z. Subjects will have a diary in which to record all analgesics, including nonsteroidal anti-inflammatory drugs and prescription analgesics, taken from the 14-day period before the first dose of the study drug to the Post-treatment visit.
aa. The morning dose of the study drug should be administered at the site on the indicated days.
bb. After the patient has provided signed informed consent; Aes are monitored throughout the study via safety assessments, observation, and patient reporting.
cc. If surgical resection of the tumor is performed within the designated time period (28 days for Post-Tx and 12 weeks for End of Study/Early Termination) after the last dose of the study drug, details of the surgery and its outcome should be obtained.

*: Not be performed from Protocol Version 4.0 onwards.
**: From Protocol Version 4.0 onwards, only local review will be performed, and central review will not be performed.

Table 1.2: Schedule of Assessments (Part 2: from the Screening Period to Cycle 7 Day 1)

		SCR	C1				C2				C3		C4	C5	C6	C7[b]	Post Treat.[c]	End St/Ear.Term.[d]	LTFU[e]
	Day	-42[a] to -1	1	8	15	22	1	8	15	22	1	15	1	1	1	1			
	Week		1	2	3	4	5	6	7	8	9	11	13	17	21	25			
	Window			±2d	±2d	±2d	±2d	±2d	±2d	±2d	±7d	±7d	±7d	±7d	±7d	±7d	±7d	±7d	±14d
Informed consent		X																	
Eligibility Assessment		X[f]																	
Demographics & medical history		X																	
Vitals	Vital signs[g]	X	X[h]		X		X				X		X	X	X	X	X		
	Height, weight	X														X[i]	X[i]		
Safety	Physical examination[j]	X					X						X			X	X		
	12-lead ECG[k]	X	X		X											X	X		
	ECHO/MUGA	X[l]																	
Laboratory Assessments	Hematology, Chemistry	X	X[m]		X[n]		X				X		X	X	X	X	X		
	Liver tests	X	X[m]	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
	Coagulation tests[o]		X[m]													X	X		
	Hepatitis panel	X																	
	Hormone testing[p]	X	X[m]													X	X		
	Serum pregnancy test	X[q]					X				X		X	X	X	X	X	X	
	Urinalysis		X[m]										X			X	X		
	SARS-CoV-2 Sample		X[h]										X			X	X		
	PK sample[r]		X		X		X				X			X					
	PK Sampling for CQ/HCQ Administration		If CQ or HCQ is administered for SARS-CoV-2, additional PK blood samples should be collected at the following visits: · Prior to the first CQ or HCQ dose (Day 1) · Day 3 or Day 4 of CQ or HCQ treatment, prior to CQ or HCQ dose (within 4h) · Last day of the CQ/HCQ treatment, prior to CQ/HCQ dose (within 4h) · The day of pexidartinib resumption, after the CQ/HCQ washout period[s], (within 8h BI of pexidartinib).																
	Biomarker Blood Sample		X[h]		X		X				X			X			X	X	
	PGx Blood Sample		X[h]																

		SCR	C1				C2				C3		C4	C5	C6	C7[b]	Post Treat.[c]	End St/Ear.Term.[d]	LTFU[e]
	Day	-42[a] to -1	1	8	15	22	1	8	15	22	1	15	1	1	1	1			
	Week		1	2	3	4	5	6	7	8	9	11	13	17	21	25			
	Window			±2d	±2d	±2d	±2d	±2d	±2d	±2d	±7d	±7d	±7d	±7d	±7d	±7d	±7d	±7d	±14d
	Tumor Biopsy sample	X[t]					X[u]										X[u]	X[u]	
	AMA[v]	X	X																
Treatment Response/ Disease Assessment	MRI of the affected joint[w]	X											X			X	X	X	
	Range of motion assessment	X											X			X	X		
	PROMIS Physical Function Scale[x]	X	X[h]								X			X		X	X		
	BPI Worst Pain NRS[x,y]	X	X[h]								X			X		X	X		
	EQ-5D-5L[x]	X	X[h]								X			X		X	X		
	Surgical Assessment Questionnaire	X														X	X		
	Analgesic use assessment[z]	X	X		X		X				X		X	X	X	X	X		
	Photographic documentation of tumor	X											X			X	X	X	
Study Drug	Dispense study Tx		X		X	X	X	X	X	X	X	X	X	X	X	X			
	Study drug dosing at site[aa]		X		X		X				X			X		X			
	Tx compliance assessment				X	X	X	X	X	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		
Adverse events[bb]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Collection of surgical data[cc]																	X	X	
Long-term follow-up questionnaire																			X

AE = adverse event; ALT = alanine aminotransferase; AMA = anti-mitochondrial antibody; AST = aspartate aminotransferase; BPI = brief pain inventory; C = cycle; D/d = Day; CQ = chloroquine; ECG = electrocardiogram; End St./Ear. Term. = end of study/early termination; EQ-5D-5L = The five-level version of EuroQol five-dimensional questionnaire; FSH = follicle-stimulating hormone; HCQ = hydroxychloroquine; incl. = including; LTFU = long-term follow-up; MRI = magnetic resonance imaging; MUGA = multigated acquisition; NRS = numeric rating scale; Pdy = pharmacodynamic(s); PGx = pharmacogenomic(s); PK =

pharmacokinetic(s); PROMIS = patient-reported outcomes measurement information system; Pt = patient; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; SCR = screening; 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 the 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 C7D1 applies to patients who are continuing or not continuing the study.
c. 28 days after the last study drug administration. Patients who exit the study with radiologic disease progression will undergo their last study evaluation at 28 ± 7 days after their last dose of the 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. Last dosing +12 weeks or before new treatment. Patients who end their study participation with no radiologic disease progression will undergo post-treatment procedures at 28 ± 7 days after their last dose of the study drug and a final MRI at 12 weeks ± 7 days after their last dose of the 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. Every 6 months after the End of Study/Early Termination.
f. Time frame between enrollment and the first dose of the study drug can be up to 3 days prior to C1D1.
g. Vital signs including blood pressure, pulse rate, and temperature should be performed before any invasive procedures are carried out on the same day.
h. Before the first dose of the study drug.
i. Weight only.
j. In the event of early withdrawal, a physical examination is performed at the Post-treatment visit.
k. A standard 12-lead ECG is performed prior to dosing. Patients should be told not to take their morning dose of the 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 instruction at the site. 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.
l. Within 21 days before the first dose of the study drug.
m. Within 72 hours before the first dose of the study drug.
n. Hematology only.
o. Patients receiving concomitant warfarin should have their anti-coagulation status carefully monitored for any necessary dose adjustments.
p. Women who are not using hormonal contraception must be tested for levels of FSH, luteinizing hormone (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.
q. Women of childbearing potential must have a serum pregnancy test within 14 days before enrollment.
r. Details on blood sampling are found in Section 8.5.
s. A washout period of no less than 14 days is required before restarting pexidartinib.

t. Must be collected during screening. A tumor biopsy that was recently collected may be substituted for the biopsy collected during screening (an archived tissue sample may be acceptable upon sponsor's/designee approval). A screening biopsy should only be collected after all other eligibility criteria are met.
u. Optional.
v. A serum sample should be collected for AMA at screening and when severe hepatotoxicity is observed.
w. MRI of the affected joint should be performed within 56 days before the first dose of the study drug.
x. Before any invasive procedures on the same day, PROMIS Physical Function Scale, BPI Worst Pain NRS, and EQ-5D-5L are to be recorded.
y. Subjects will complete the BPI Worst Pain NRS item for seven consecutive days prior to C1D1, C3D1, C5D1, C7D1 and Post-Tx, as well as on the day of the study visit. In addition, subjects will complete the BPI Worst Pain NRS item on an outpatient basis prior to the indicated study visits.
z. Subjects will have a diary in which to record all analgesics, including nonsteroidal anti-inflammatory drugs and prescription analgesics, taken from the 14-day period before the first dose of the study drug to the Post-treatment visit.
aa. The morning dose of the study drug should be administered at the site on the indicated days.
bb. After the patient has provided signed informed consent; AEs are monitored throughout the study via safety assessments, observation, and patient reporting.
cc. If surgical resection of the tumor is performed within the designated time period (28 days for Post-Tx and 12 weeks for End of Study/Early Termination) after the last dose of the study drug, details of the surgery and its outcome should be obtained.

Table 1.3: Schedule of Assessments (Parts 1 and 2: Study drug continuation after Cycle 7 Day 1)

		C10+[a]	Post Tx[b]	End St/Ear.Term.[c]	LTFU[d]
	Day	1			
	Week	37+			
	Window	±7d	±7d	±7d	±14d
Vitals	Vital signs[e]	X	X		
	Weight		X		
Safety	Physical examination[f]	X	X		
	12-lead ECG		X		
Laboratory Assessments	Hematology, Chemistry	X	X		
	Liver tests	X	X		
	Coagulation tests[g]		X		
	Hormone testing[h]		X		
	Serum pregnancy test	X	X	X	
	Urinalysis		X		
	SARS-CoV-2 Sample	X	X		
	PK Sampling for CQ/HCQ Administration	If CQ or HCQ is administered for SARS-CoV-2, additional PK blood samples should be collected at the following visits: · Prior to the first CQ or HCQ dose (Day 1) · Day 3 or Day 4 of CQ or HCQ treatment, prior to CQ or HCQ dose (within 4h) · Last day of the CQ/HCQ treatment, prior to CQ/HCQ dose (within 4h) · The day of pexidartinib resumption, after the CQ/HCQ washout period[i], (within 8h BI of pexidartinib).			
	Biomarker Blood Sample		X*	X*	
	Tumor Biopsy sample		X[j,*]	X[j,*]	
	AMA[k]	X			
Treatment Response/ Disease Assessment	MRI of the affected joint**	X***	X	X	
	Range of motion assessment	X*	X*		
	PROMIS Physical Function Scale[l]	X*	X*		
	BPI Worst Pain NRS[l,m]	X*	X*		

		C10+[a]	Post Tx[b]	End St/Ear.Term.[c]	LTFU[d]
	Day	1			
	Week	37+			
	Window	±7d	±7d	±7d	±14d
	EQ-5D-5L[l]	X*	X*		
	Surgical Assessment Questionnaire		X*		
	Analgesic use assessment	X*	X*		
	Photographic documentation of tumor	X*	X*	X*	
Study Drug	Dispense study Tx	X			
	Tx compliance assessment	X			
Concomitant medications		X	X		
Adverse events		X	X		
Collection of surgical data[a]			X	X	
Long-term follow-up questionnaire					X*

AE = adverse event; ALT = alanine aminotransferase; AMA = Anti-mitochondrial antibody; AST = aspartate aminotransferase; BPI = brief pain inventory; C = cycle; D/d = Day; CQ = chloroquine; ECG = electrocardiogram; End St./Ear. Term. = end of study/early termination; EQ-5D-5L = The five-level version of EuroQol five-dimensional questionnaire; FSH = follicle-stimulating hormone; HCQ = hydroxychloroquine; incl. = including; LTFU = long-term follow-up; MRI = magnetic resonance imaging; NRS = numeric rating scale; Pdy = pharmacodynamic(s); PGx = pharmacogenomic(s); PK = pharmacokinetic(s); PROMIS = patient-reported outcomes measurement information system; Pt = patient; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2;TGCT = tenosynovial giant cell tumor; Tx = treatment.

a. The procedures are performed on C10D1 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 at 28 ± 7 days after their last dose of the 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 at 28 ± 7 days after their last dose of the study drug and a final MRI at 12 weeks ± 7 days after their last dose of the 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. Every 6 months after the End of Study/Early Termination.
e. Vital signs should be measured before any invasive procedures are carried out on the same day.
f. In the event of early withdrawal, a physical examination is performed at the Post-treatment visit.
g. Patients receiving concomitant warfarin should have their anti-coagulation status carefully monitored for any necessary dose adjustments.

h. Women who are not using hormonal contraception must be tested for levels of FSH, luteinizing hormone (LH), progesterone, and estradiol. Hormone testing will not be required for women who have either had an oophorectomy or are post-menopausal.
i. A washout period of no less than 14 days is required before restarting pexidartinib.
j. Optional.
k. A serum sample should be collected for AMA when severe hepatotoxicity is observed.
l. Before any invasive procedures on the same day, PROMIS Physical Function Scale, BPI Worst Pain NRS, and EQ-5D-5L are to be recorded.
m. Subjects will complete the BPI Worst Pain NRS item for seven consecutive days prior to the indicated study visits, as well as on the day of the study visit. In addition, subjects will complete the BPI Worst Pain NRS item on an outpatient basis prior to the indicated study visits.
n. If surgical resection of the tumor is performed within the designated time period (28 days for Post-Tx and 12 weeks for End of Study/Early Termination) after the last dose of the study drug, details of the surgery and its outcome should be obtained.

*: Not be performed from Protocol Version 4.0 onwards.
**: From Protocol Version 4.0 onwards, only local review will be performed, and central review will not be performed.
***: MRI are performed every 24 weeks from Protocol Version 4.0 onwards.

2. INTRODUCTION

2.1. Background

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.

2.1.1. Tenosynovial giant cell tumor

Tenosynovial giant cell tumor (TGCT) is a rare, nonmalignant neoplasm of the synovium, bursae, or tendon sheaths, generally affecting young adults (<40 years of age) of both sexes.[2] 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 (ROM) 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.[2,3] 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.[2,3] 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.[2,4,5] A more recent survey in Denmark demonstrates an incidence of 4.4 per million population for localized TGCT and 1.2 per million population for diffuse TGCT,[3] 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.[6]

TGCT predominantly consists 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), which is 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.[7] 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 as complete surgical resection of the tumor 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 in patients with focal disease is low, ranging from 0% to 6%[2]; however, in patients with diffuse forms of the disease,

recurrence is considerably more common, and is estimated to be in a range of 40%.[8] 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 the removal of major tendons or neurovascular structures, leading to significant postsurgical morbidity. Limb amputation may be required in severe, recurrent cases.[2]

No systemic antitumor agents have been approved for this indication in Japan.[9] Anti-inflammatory and analgesic medications, including opioids, are 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.

2.1.2. Pexidartinib (PLX3397)

Pexidartinib is a small molecule tyrosine kinase inhibitor that targets CSF1R, KIT proto-oncogene receptor tyrosine kinase (KIT), and feline McDonough Sarcoma-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 in vitro. 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 not amenable to improvement with surgery.

2.2. Study Rationale

Clinical Experience

PLX108-10 (ENLIVEN Study): Pexidartinib or Placebo in Subjects with Tenosynovial Giant Cell Tumor

The ENLIVEN study was 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 twice a day {BID} or placebo for 22 weeks]. The subjects who completed Part 1 (ie, 24 weeks of dosing) were eligible to advance to Part 2, a long-term treatment phase where all subjects would receive open-label pexidartinib at a maximum starting dose of 800 mg/day.

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

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

As of the data cut-off date of 31 Jan 2018, frequent treatment-emergent adverse events (TEAEs) (>20%) for subjects treated with pexidartinib in Part 1 were hair color changes (pexidartinib arm vs placebo arm: 67.2% vs 3.4%); fatigue (54.1% vs 35.6%); AST increased (39.3% vs 0%);

nausea (37.7% vs 40.7%); ALT increased (27.9% vs 1.7%); dysgeusia (24.6% vs 1.7%); arthralgia (23.0% vs 25.4%). Generally, the frequency of TEAEs in pexidartinib-treated subjects in Part 1 and Part 2 was only slightly greater than the frequency in Part 1 only, demonstrating that few new TEAEs occurred with long-term pexidartinib treatment. Most TEAEs occurred in the first 12 weeks of pexidartinib treatment. Please refer to the most recent IB for additional information.[10]

2.2.1. Study Rationale

The principal data supporting the efficacy of pexidartinib in TGCT have been indicated in the phase 3 study (Study PLX108-10 [ENLIVEN], N = 120) conducted in the US, Canada, European countries, and Australia. Pexidartinib was approved for adult patients with symptomatic TGCT associated with severe morbidity or functional limitations and not amenable to improvement with surgery by the US Food and Drug Administration (FDA) on 2 August 2019.

No systemic antitumor agents are approved for TGCT in Japan. A systemic therapy that provides a meaningful clinical benefit for TGCT patients is highly needed.

Similar safety, pharmacokinetics (PK), and efficacy as the ENLIVEN study can be expected in this Japan phase 2 study because there are no differences between the study populations of TGCT subjects in the ENLIVEN study and this Japanese phase 2 study in terms of extrinsic factors such as disease definition, diagnosis, medical practice and therapeutic approach. Regarding intrinsic ethnic factors, there is currently no evidence to indicate that the populations are not similar. Pexidartinib has the potential to offer a treatment option for TGCT patients in Japan.

2.3. Benefit and Risk Assessment

Pexidartinib has been approved in the US for the treatment of TGCT associated with severe morbidity or functional limitations and not amenable to improvement with surgery.

Safety data from nonclinical studies, clinical studies, and non-interventional studies have been reviewed. Hepatotoxicity is an important identified risk, and both embryo-fetal toxicity and fertility toxicity are considered an important potential risk with pexidartinib. In repeated dose toxicity studies in rats and dogs, male rats and dogs displayed testicular toxicity. Following a 16-week recovery period, testicular toxicity persisted in rats and partially recovered in dogs, but did not fully recover. Serious and prolonged hepatotoxicity with ductopenia and/or cholestasis has been observed in subjects treated with pexidartinib. Cases of cholestasis have been observed in the first 8 weeks and have generally resolved with treatment discontinuation, but in some cases have been severe, with a protracted course requiring liver dialysis and, in 1 case, transplantation. Hepatotoxicity may be fatal. One fatal case with ongoing cholestatic liver injury at the time of death has been reported. The mechanism of cholestatic hepatotoxicity is unknown, and its occurrence cannot be predicted. Protocol-defined dose reductions and discontinuations of pexidartinib, increased frequency of laboratory monitoring, and reporting of findings should be followed. In addition, rechallenge with pexidartinib should not be attempted. Risk minimization measures, such as frequent monitoring during the first 8 weeks of pexidartinib treatment related to managing these risks, should be conducted. Please refer to the most recent IB for additional information.[10]

3. OBJECTIVES, OUTCOME MEASURES, AND ENDPOINTS

The objectives, definitions of associated endpoints as well as applicable outcome measures are described in Table 3.1. Further requirements for the endpoint analyses and censoring rules, where applicable, can be found in Section 9.5.1, Section 9.5.2, Section 9.5.3, and Section 9.5.4.

Table 3.1: Description of Objectives, Outcome Measures, and Endpoints

Objectives	Outcome Measure	Endpoints	Category
Primary			
Part 1: To evaluate the tolerability and PK of pexidartinib in Japanese subjects	**Title:** DLT **Description:** Number of subjects with DLTs **Time frame:** C1D1 to C1D28	Number of subjects with DLTs	Safety
	Title: PK profile **Description:** Plasma concentrations and PK parameters of pexidartinib and ZAAD-1006a, the major metabolite of pexidartinib **Time frame:** C1D1-C1D2 and C1D15 (with intensive sampling)	Plasma concentrations and PK parameters of pexidartinib and ZAAD-1006a, the major metabolite of pexidartinib	PK
Part 2: To evaluate the efficacy of pexidartinib in Japanese subjects	**Title:** ORR based on RECIST 1.1 **Description:** ORR as assessed by centrally reviewed MRI scan based on RECIST 1.1 **Time frame:** Week 25	ORR is defined as the proportion of subjects who achieved a CR or PR based on RECIST 1.1 by centrally reviewed MRI scan. No confirmation (ie, CR or PR at the subsequent MRI assessment) will be required for a CR or PR.	Efficacy
Secondary			
Part 2: To evaluate the efficacy of pexidartinib	**Title:** ORR based on TVS **Description:** ORR as assessed by centrally reviewed MRI scan based on TVS **Time frame:** Week 25	ORR is defined as the proportion of subjects who achieved a CR or PR based on TVS by centrally reviewed MRI scan	Efficacy
	Title: ROM **Description:** Raw measurements of the affected joint with a goniometer **Time frame:** Week 25	Mean change from baseline in ROM of the affected joint, relative to a reference standard for the same joint	Efficacy
	Title: PROMIS Physical Function Scale **Description:** PRO relevant to the assessment of lower and upper limb function **Time frame:** Week 25	Mean change from baseline score in the PROMIS Physical Function Scale	Efficacy
	Title: BPI Worst Pain NRS	Proportion of responders based on the BPI Worst Pain NRS item and analgesic use by BPI-30 definition	Efficacy

Objectives	Outcome Measure	Endpoints	Category
	Description: PRO relevant to the assessment of the "worst" pain in the last 24 hours **Time frame:** Week 25	(ie, 30% or more improvement in average NRS)	
	Title: BOR based on RECIST 1.1 **Description:** BOR as assessed by centrally reviewed MRI scan based on RECIST 1.1 **Time frame:** At the time of the primary analysis: After all subjects have made the Week 25 visit or have discontinued from the study, whichever occurs first	BOR is defined as the proportion of subjects who achieved CR, PR, SD, PD, and NE recorded as the best response based on RECIST 1.1 by centrally reviewed MRI scan	Efficacy
	Title: BOR based on TVS **Description:** BOR as assessed by centrally reviewed MRI scan based on TVS **Time frame:** At the time of the primary analysis	BOR is defined as the proportion of subjects who achieved CR, PR, SD, PD, and NE recorded as the best response based on TVS by centrally reviewed MRI scan	Efficacy
	Title: DoR based on RECIST 1.1 **Description:** DoR as assessed by centrally reviewed MRI scan based on RECIST 1.1 **Time frame:** At the time of the primary analysis	DoR is defined as the time from the date of the first recorded response to the first date of documented disease progression	Efficacy
	Title: DoR based on TVS **Description:** DoR as assessed by centrally reviewed MRI scan based on TVS **Time frame:** At the time of the primary analysis	DoR is defined as the time from the date of the first recorded response to the first date of documented disease progression	Efficacy
Part 1, Part 2: To assess the safety of pexidartinib	**Title:** TEAEs and other safety parameters during the study* **Description:** Descriptive statistics of safety endpoints **Time frame:** Continuous monitoring and reported at the time of each data cut-off *Though this is a secondary objective, this is a primary outcome measure	Safety evaluation include the following, but is not limited to: TEAEs, drug induced hepatotoxicity, laboratory tests, vital signs, and ECGs	Safety
Part 1, Part 2: To evaluate the PK properties of pexidartinib	**Title:** PK profile **Description:** Plasma concentrations and PK parameters of pexidartinib and ZAAD-1006a	Plasma concentrations and PK parameters of pexidartinib and ZAAD-1006a, the major metabolite of pexidartinib	PK

Objectives	Outcome Measure	Endpoints	Category
	Time frame: Part 1; C2D1, C3D1, and C5D1 (with sparse sampling), Part 2; C1D1-C1D2 and C1D15 (with intensive sampling) and C2D1, C3D1, C5D1 (with sparse sampling)		
Exploratory			
Part 2: To evaluate the efficacy of pexidartinib	**Title:** ORR based on RECIST 1.1 **Description:** ORR as assessed by locally reviewed MRI scan based on RECIST 1.1 **Time frame:** Week 25	Proportion of subjects who achieve a CR or PR of pexidartinib based on RECIST 1.1 at Week 25 by locally reviewed MRI scan	Efficacy
	Title: Tumor response based on modified RECIST 1.1-sum of the short-axis dimension (SSD) **Description:** Tumor response as assessed by centrally reviewed MRI scan based on modified RECIST 1.1-SSD **Time frame:** Week 25	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	Efficacy
	Title: EQ-5D-5L **Description:** Mean change from baseline score in the EQ-5D-5L at Week 25 **Time frame:** Week 25	Mean change from baseline score in the EQ-5D-5L at Week 25	Efficacy
	Title: BOR based on RECIST 1.1 **Description:** BOR as assessed by locally reviewed MRI scan based on RECIST 1.1 **Time frame:** At the time of the primary analysis	BOR is defined as the proportion of subjects who achieved CR, PR, SD, PD, and NE recorded as the best response based on RECIST 1.1 by locally reviewed MRI scan	Efficacy
	Title: DoR based on RECIST 1.1 **Description:** DoR as assessed by locally reviewed MRI scan based on RECIST 1.1 **Time frame:** At the time of the primary analysis	DoR is defined as the time from the date of the first recorded response to the first date of documented disease progression	Efficacy
	Title: DoR based on modified RECIST 1.1-SSD **Description:** DoR as assessed by centrally reviewed MRI scan based on modified RECIST 1.1-SSD **Time frame:** At the time of the primary analysis	DoR is defined as the time from the date of the first recorded response to the first date of documented disease progression	Efficacy

Objectives	Outcome Measure	Endpoints	Category
	Title: Photographic documentation **Description:** Photographs of tumor appearance **Time frame:** At the time of the primary analysis	Change in appearance of tumor by photographs from baseline to the time of analysis	Efficacy
	Title: Surgical Assessment Questionnaire **Description:** Assessment of the surgical status **Time frame:** At the time of the primary analysis	Results of the Surgical Assessment Questionnaire	Efficacy
	Title: Long-term subject status **Description:** Assessment of subject status during the follow-up period by telephone contact **Time frame:** At the time of the primary analysis	Results of the LTFU questionnaire after the end of study or early termination visit	Efficacy
Part 1: To evaluate the efficacy of pexidartinib	The outcome measures planned for assessing the efficacy of the primary objectives, the secondary objectives, and the exploratory objectives		Efficacy
To characterize associated biomarkers in peripheral blood and tumor tissue that may predict the efficacy and safety of pexidartinib	Not applicable	Relationship between clinical outcome and • Plasma CSF-1 and IL-34 concentrations (ELISA) • CSF1R gene mutations (NGS) • Profile of drug-metabolizing enzyme and transporter gene mutations (PharmacoScan™ assay) • Profile of tumor-infiltrating immune cells (immunohistochemistry) • Profile of immune cells in peripheral blood (flow cytometry) • CSF-1 rearrangements (FISH, DNA sequencing or RNA sequencing) Subject's samples will be banked for future biomarker analyses, which may include comprehensive gene mutation and gene expression profiling with NGS and RNA-sequencing	Biomarkers/ PGx

BOR = best overall response; BPI = brief pain inventory; C = cycle; CR = complete response; D = Day; DLT = dose-limiting toxicity; DoR = duration of response; ECG = electrocardiogram; ELISA = enzyme-linked immunosorbent assay; EQ-5D-5L = The five-level version of EuroQol five-dimensional questionnaire; FISH = fluorescence in situ hybridization; LTFU = long-term follow-up; MRI = magnetic resonance imaging; NGS = next

generation sequencing; NE = not evaluable; NRS = numeric rating scale; ORR = objective response rate; PD = progressive disease; PGx = pharmacogenomics; PK= pharmacokinetics; PR = partial response; PRO = patient-reported outcomes; PROMIS = patient-reported outcomes measurement information system; RECIST= response evaluation criteria in solid tumors; ROM = range of motion; SD = stable disease; SSD = sum of the short-axis dimension; TEAE = treatment-emergent adverse event; TVS = tumor volume score

3.1. Rationale for Selection of Primary and Key Secondary Endpoints

The primary endpoint of Part 1 will be the dose-limiting toxicities (DLTs) evaluation and PK profiles to evaluate the tolerability and PK of pexidartinib in Japanese subjects.

The primary endpoint of Part 2 will be the ORR, defined as the proportion of subjects who achieve a complete response (CR) or partial response (PR) based on Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1) and assessed by centrally reviewed MRI scan. Confirmation will not be required for CR or PR.[11] The ORR is a direct measure of the drug antitumor activity. Since ORR is directly attributable to the drug effect, it is an appropriate measure of efficacy in studies without a comparator.[12] The efficacy of pexidartinib in TGCT was evaluated with same primary endpoint in the ENLIVEN study.

The study hypotheses of Part 2 is that the ORR of the primary endpoint exceeds the ORR of 5% of the placebo arm in the ENLIVEN study. The assumed ORR of the primary endpoint is 37.7% of the pexidartinib arm in the ENLIVEN study.

It is considered that tumor shrinkage is essential to improve symptoms of advanced TGCT subjects. The improvement of symptoms will be evaluated with secondary endpoints. The endpoint of TVS using central MRI readers will be reinforced for the primary imaging endpoint of RECIST 1.1 assessment. The endpoint of ROM, the Patient-Reported Outcomes Measurement Information System (PROMIS) Physical Function Scale, the Brief Pain Inventory (BPI) Worst Pain Numeric Rating Scale (NRS) Item will reinforce the explanation of clinical benefit from the primary imaging endpoint.

4. STUDY DESIGN

4.1. Overall Design

This is a phase 2, multicenter, two-part, open-label, single-arm study, conducted in Japan, which is aimed to evaluate the tolerability, safety, efficacy, and PK of pexidartinib in adult subjects with symptomatic TGCT associated with severe morbidity or functional limitation and not amenable to improvement with surgery. It is planned to conduct this study at approximately 5 study sites located in Japan. The subject population is described in Section 5.

The study start date is the date when the first subject has signed informed consent. A subject is eligible to be enrolled into the interventional phase of the study when the Investigator or designee has determined that all inclusion and exclusion criteria have been satisfied, including having obtained written informed consent.

Enrollment is defined as the timepoint at which the Investigator has obtained the subject identifier (SID) in the interactive response technology (IRT) and the study drug has been assigned.

4.1.1. Design Overview

This study consists of 2 parts: In Part 1, the tolerability and PK of pexidartinib 800 mg/day (400 mg BID) given on an empty stomach will be evaluated to determine the initiation of Part 2, and in Part 2, the efficacy, safety and PK of pexidartinib 800 mg/day given on an empty stomach will be evaluated.

Part 1:

Three or six eligible subjects will be enrolled in Part 1. Part 1 will be divided into 3 periods: Screening Period, Treatment Period, and Follow-up Period (which includes the Long-term Follow-up [LTFU]):

At the beginning of the Screening Period subjects sign the informed consent form (ICF). During the 28-day Screening Period, subjects' eligibility will be confirmed. They will undergo medical history evaluation, physical examination, vital sign determination, laboratory assessments, and electrocardiogram (ECG), echocardiogram (ECHO) or multigated acquisition (MUGA) scan.

The Treatment Period starts on Cycle 1 Day 1 (C1D1) and continues until a subject permanently discontinues pexidartinib (Section 7.1). During the Treatment Period, pexidartinib will be administered at 400 mg once (2 capsules in the morning) on C1D1 to evaluate the PK profile for 24 hours. From C1D2 and after, pexidartinib will be administered at 400 mg BID (2 capsules in the morning and 2 capsules in the evening). Pexidartinib must be administered on an empty stomach (at least 1 hour before or 2 hours after a meal or snack), at approximately the same times of the day, and approximately 12 hours apart. Subjects will be hospitalized from C1D1 to C1D2 in Part 1 to allow for careful safety monitoring. Discharge will be decided at the Investigator's discretion. The Investigator should examine the subject carefully before deciding to discharge. The study site should educate the subject about an emergency contact. Additional safety assessments should be conducted as needed, at the Investigator's discretion. The second subject should start dosing at least 24 hours after the initial dosing of the first subject.

After study treatment is discontinued, subjects will be followed for 28 ± 7 days for safety. Subjects will then enter LTFU for collection of information on subsequent treatment.

The subject population is described in Section 5.

Evaluation of tolerability is based on review of all DLT-evaluable subjects who have received pexidartinib and have either completed the minimum safety evaluation requirements over the DLT evaluation period (28 days) or have experienced a DLT during the DLT evaluation period. If a DLT is observed in 1 of 3 subjects, at least 6 subjects in total will be treated in Part 1. If a DLT is observed in 0 of 3 subjects or l of 6 subjects in Part 1, Part 2 will be initiated. If a DLT is observed in ≥2 of 3 subjects or ≥2 of 6 subjects in Part 1, the safety monitoring committee (SMC) will discuss whether more subjects should be added to Part 1. Transition to Part 2 will be considered based on review of the tolerability, available safety and PK data from Part 1 including subjects who are not considered to be DLT-evaluable subjects for any other reason than a DLT.

Part 2:

Part 2 will begin after completing evaluation of tolerability and PK in Part 1. Fifteen eligible subjects will be enrolled in Part 2. Part 2 will be divided into 3 periods: Screening Period, Treatment Period, and Follow-up Period (which includes the LTFU):

At the beginning of the Screening Period subjects sign the ICF. During the 42-day Screening Period, subjects' eligibility will be confirmed. They will undergo medical history evaluation, physical examination, vital sign determination, laboratory assessments, and ECG, ECHO or MUGA scan.

During the Treatment Period, pexidartinib will be administered at 400 mg once (2 capsules in the morning) on C1D1 to evaluate the PK profile for 24 hours. From C1D2 and after, pexidartinib will be administered at 400 mg BID (2 capsules in the morning and 2 capsules in the evening). Pexidartinib must be administered on an empty stomach (at least 1 hour before or 2 hours after a meal or snack), at approximately the same times of the day, and approximately 12 hours apart. The Treatment Period starts on C1D1 and continues until a subject permanently discontinues pexidartinib (Section 7.1).

After study treatment is discontinued, subjects will be followed for 28 ± 7 days for safety. Subjects will then enter LTFU for collection of information on subsequent treatment.

In June 2024, the sponsor decided to halt the enrollment of participants after 9 subjects were enrolled in Part 1 and not proceed with Part 2.

4.1.2. End of Study

The **primary completion date** is the date when all enrolled subjects have completed the predetermined duration of treatment (ie, the date when all DLT-evaluable subjects have either completed minimum safety evaluation requirements over the DLT evaluation period [28 days] or have experienced a DLT during the DLT evaluation period for Part 1, Week 25 for Part 2) or have discontinued the study. This date is used as the cut-off date for the analysis of the primary endpoint of the study. All subjects still on treatment and continuing to derive benefit from the

study drug at the Primary Completion Date will continue to follow the study schedule of assessments (Section 1.3) until the **overall End of Study (EOS)** is reached.

Overall EOS will occur when:

- the last subject last visit has occurred
- all subjects have discontinued treatment or discontinued the study or have died
- an alternative study becomes available for subjects continuing to derive benefit from treatment with pexidartinib, where the study drug is offered to these subjects
- the study is discontinued by the Sponsor for other reasons (administrative, program-level, or class-related)

The subject's EOS is the date of their last study visit/contact.

4.1.3. Dose Regimen

Pexidartinib will be administered at 400 mg once (2 capsules in the morning) on C1D1 to evaluate the PK profile for 24 hours. From C1D2 and after, pexidartinib will be administered at 400 mg BID (2 capsules in the morning and 2 capsules in the evening). Pexidartinib must be administered on an empty stomach (at least 1 hour before or 2 hours after a meal or snack), at approximately the same times of the day, and approximately 12 hours apart, according to the dosage regimen outlined in Table 6.1.

4.1.4. Duration

Study duration includes three periods: Screening Period, Treatment Period and Follow-up Period (which includes the LTFU).

Duration of Treatment and Subject Participation

Subjects who experience clinical benefit will continue to receive pexidartinib in the absence of disease progression, clinical progression, unacceptable toxicity, withdrawal of consent by subject, physician decision, protocol deviation, pregnancy, lost to follow-up, study termination by the sponsor, death, or other reasons (see details in Section 7.1). Note: Only protocol deviations that are deemed significant by the investigator, with or without consultation with the sponsor, may lead to permanent study drug discontinuation.

Overall Study Duration

Enrollment was planned to occur over approximately 17 months for Part 1 and Part 2, with treatment and follow-up projected to continue for approximately 27 months after the last subject was enrolled in Part 2.

Anticipated total duration of the study was planned to be approximately 44 months.

In June 2024, the sponsor decided to halt the enrollment of participants after 9 subjects were enrolled in Part 1. For the subjects receiving the study drug in Part 1 and wish to continue

receiving it from Protocol Version 4.0 onwards, the study drug administration will be allowed to continue until February 2026.

The study will continue until the overall EOS is reached. See Section 4.1 for the definition of study start and Section 4.1.2 for the definition of the overall EOS.

Study Drug Continuation After the End of Study

Not applicable.

4.2. Rationale for Study Design

The objective of Part 1 is to evaluate the tolerability and PK of pexidartinib in Japanese TGCT subjects for further evaluation in Part 2. Evaluation of tolerability by number of subjects with DLTs in units of 3 subjects for each dose is frequently used in oncology phase 1 dose escalation studies.

The objective of Part 2 is to evaluate the safety and efficacy of pexidartinib in Japanese TGCT subjects. The principal data supporting the efficacy of pexidartinib for TGCT have been indicated in the ENLIVEN study conducted in the US, Canada, European countries, and Australia. Therefore, the design of Part 2 will be similar to the design of the ENLIVEN study.

4.3. Justification for Dose

In the phase 1 study conducted in the US (PLX108-01 study), pexidartinib 1000 mg/day given on an empty stomach was identified as the maximum-tolerated dose (MTD) when given to solid tumor subjects. In the phase 1 study conducted in Taiwan (PL3397-A-A103 study), pexidartinib was also administered at 600 mg/day or 1000 mg/day for the first 2 weeks followed by 800 mg/day given on an empty stomach in solid tumor subjects. Pexidartinib 1000 mg/day given on an empty stomach was identified as the MTD in Study PL3397-A-A103.

The dose regimen of this study, pexidartinib 800 mg/day (400 mg BID) given on an empty stomach, is revised from the dose regimen of 1000 mg/day for 2 weeks followed by 800 mg/day (400 mg BID) used in Part 1 of the ENLIVEN study and is the same as the FDA-approved dose regimen in the US.

5. STUDY POPULATION

5.1. Inclusion Criteria

Subjects must meet all of the following criteria to be eligible for enrollment into the study:

1. Sign and date the ICF, prior to the start of any study- specific qualification procedures.
2. Age ≥20 years.
3. A diagnosis of TGCT (i) that has been histologically confirmed by a pathologist[1] 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).

4. 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.
5. Stable prescription of analgesic regimen during the 2 weeks prior to enrollment.
6. Adequate hematologic, hepatic, and renal function, defined by:
    a. Absolute neutrophil count $\geq 1.5 \times 10^9$/L
    b. Hemoglobin >10 g/dL
    c. Platelet count $\geq 100 \times 10^9$/L
    d. AST and ALT ≤1.0 ×upper limit of normal (ULN)
    e. Total bilirubin and direct bilirubin ≤1.0 × ULN
    f. ALP ≤1.0 × ULN
    g. Creatinine clearance (CL_{CR}) >15 mL/min.
7. If the subject is a female of childbearing potential, she must have a negative serum pregnancy test within 14 days before enrollment and must be willing to use highly effective birth control with a non-hormonal method of contraception, as detailed in Section 10.3.4, upon enrollment, during the Treatment Period, and for 1 month following the last dose of study drug. A female is considered of childbearing potential following menarche and until becoming postmenopausal (no menstrual period for a minimum of 12 months and a follicle-stimulating hormone [FSH] level>40 mIU/mL) unless permanently sterile (undergone a hysterectomy, bilateral salpingectomy or bilateral oophorectomy).
8. If male, the subject must be surgically sterile or willing to use highly effective birth control (Section 10.3.4) upon enrollment, during the treatment period, and for 1 month following the last dose of study drug.
9. Male subjects must not freeze or donate sperm starting at Screening and throughout the study period, and at least 1 month after the final study drug administration.
10. Female subjects must not donate, or retrieve for their own use, ova from the time of screening and throughout the study treatment period, and for at least 1 month after the final study drug administration.
11. Willingness and ability to undergo tumor biopsy at screening or willingness to provide archived tissue samples for assessment of biomarkers.
12. Willingness and ability to complete the PROMIS Physical Function Scale and the BPI Worst Pain NRS Item.
13. Willingness and ability to record a paper diary.

5.2. Exclusion Criteria

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

1. Inadequate washout period before enrollment, defined as:
    - Investigational drug/device use within < 28 days.
2. Previous use of pexidartinib or any selective treatment targeting CSF-1 or the CSF1R; previous use of oral multi-kinase inhibitors (eg, imatinib or nilotinib) are allowed.

3. Active cancer, except for the tumor for which the subject is enrolled in the study, (either concurrent or within the last year of starting the 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, chronic, inactive carrier, or resolved hepatitis C or hepatitis B infection, except for patients only positive for HBs antibody (HBs antigen negative and HBc antibody negative) and with clear prior vaccination. Or known active or chronic infection with the human immunodeficiency virus.
6. Pre-existing increased serum transaminases; total bilirubin or direct bilirubin (>ULN); or active liver or biliary tract disease, including increased ALP.
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 potassium-competitive acid blockers (P-CABs), or other products known to cause hepatotoxicity.
10. Women who are breastfeeding or intends to breast-feed from the time of screening and throughout the study treatment period, and for at least 2 weeks after the final study drug administration.
11. Uncontrolled or significant cardiovascular disease, including:
    a. QT interval corrected with Fridericia’s formula (QTcF) interval >450 ms (men, average of triplicate determinations) or >470 ms (women, average of triplicate determinations);
    b. Myocardial infarction within 6 months prior to screening;
    c. Uncontrolled angina pectoris within 6 months prior to screening;
    d. New York Heart Association (NYHA) Class 3 or 4 congestive heart failure;
    e. Left ventricular ejection fraction (LVEF) < 50% or institutional lower limit of normal
    f. Uncontrolled hypertension (resting systolic blood pressure >180 mmHg or diastolic blood pressure >110 mmHg).
12. MRI contraindications.
13. History of hypersensitivity to any excipients in the investigational product.
14. Inability to swallow capsules.

5.3. Screening Failures, Rescreening, and Subject Replacement

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 in the screening log. However, it may not be necessary to repeat MRI, ROM and surgical assessment following consultation with the Daiichi Sankyo (DS) Medical Monitor. Subjects who are withdrawn from the study prior to completing Cycle 1 of Part 1 for any other reason than a DLT will be replaced. Identification numbers may not be re-used. Subjects who receive < 75% of the planned dose during the DLT evaluation period for any other reason than a DLT will not be considered evaluable and must be replaced in Part 1. Subjects withdrawn from the study after Cycle 2 of Part 1 and later or Part 2 will not be replaced.

6. STUDY TREATMENT(S)

6.1. Study Drug(s) Description

Table 6.1 describes the formulation, dose, regimen, duration, packaging, and labeling of pexidartinib.

Table 6.1: Study Drug Dosing Information

Study Drug Name	**PLX3397**
Dosage Formulation	Capsules
Dosage Level(s)	800 mg/day
Route of Administration	Oral
Dosing	400 mg BID (2 capsules in the morning and 2 capsules in the evening). The study drug must be taken on an empty stomach (at least 1 hour before or 2 hours after a meal or snack) at approximately the same time of the day with an approximate 12-hour interval.
Duration	Continuous dosing
Packaging	Bottles (35 capsules per bottle) Packaging will clearly display the name of the product, storage conditions, and other required information as applicable in accordance with the local regulations
Labeling	Bottles will be labeled as required per local regulatory requirement

BID = twice a day

6.2. Preparation, Handling, Storage, and Accountability for Study Drug(s)

Preparation, Handling, and Disposal

The preparation of study drug will be conducted in accordance with the Pharmacy Manual provided by the Sponsor.

Procedures for proper handling and disposal should be followed in compliance with the standard operating procedures (SOP) of the site.

Administration

The study drug will only be given to enrolled subjects under the supervision of the principal investigator or identified subinvestigator(s). 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 Part 1 or Part 2 in the morning. At this visit, subjects will be instructed to take 400 mg at the C1D1 visit and 400 mg BID for a total daily dose of 800 mg (2 capsules in the morning and 2 capsules in the evening) from C1D2 and thereafter. The study drug must be taken on an empty stomach at approximately the same time of the day with an approximate 12-hour interval. Each dosing cycle will be 28 days.

For the C1D15 visit (Week 3) and any visit when an ECG and PK will be performed, subjects must be told NOT to take their morning dose of the study drug before coming for the study visit,

which should be scheduled in the morning. The subject must be instructed to bring their bottle of the study drug to the site and take their morning dose upon instruction at the study site. The time of dosing must be recorded. Subjects will then take their evening dose at home. If the dose administered at the site is taken in the afternoon, the subject must be instructed to skip the evening dose for that day.

For the C7D1 visit (Week 25), subjects must be told NOT to take the morning dose of the 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 the 24-week treatment, ie, a maximum dose of 800 mg/day pexidartinib.

Between site visits, subjects must take their study drug at home and record the dosing information in the study dosing diary. Missed doses (generally those outside a ± 2-hour dosing window) must be skipped and NOT be taken as a double dose at the next dosing time point. Subjects who vomit their dose must be instructed NOT to make up that dose.

Storage

The study drug (pexidartinib) must be stored in a secure, limited access storage area under the recommended storage conditions noted on the label. The study drug must be stored at a temperature of up to 25°C. Excursion is permitted up to 30°C. Subjects must be instructed to store the study drugs at room temperature out of the reach of children or other cohabitants.

If storage conditions are not maintained per specified requirements, then the Sponsor or contract research organization (CRO) should be contacted.

Drug Accountability

When a drug shipment is received, the Investigator or designee will check the amount and condition of the drug against the shipping documentation.

The Receipt of Shipment Form should be faxed as instructed on the form unless receipt is controlled by IRT.

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

The Investigator is responsible for study drug accountability, reconciliation and record maintenance (ie, Receipt of Shipment Form, dispensation/return record, and certificate of destruction/return receipt).

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 the study drug received; the subject's identification number or supply number as applicable, for whom the study drug was dispensed; the date and quantity of the 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 the designee as instructed by DS. The study drug will be returned only after the study monitor has completed a final inventory to verify the quantity to be returned. Return of the 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 the 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.

6.3. Measure to Minimize Bias: Randomization and Blinding

Method of Treatment Allocation

This will be an open-label study. All subjects will be receiving pexidartinib. The second subject of Part 1 should start dosing at least 24 hours after the initial dosing of the first subject. Part 2 will begin after completing evaluation of tolerability and PK of pexidartinib in Part 1.

Blinding

This study has an open-label design, and no blinding will be performed.

6.4. Treatment Compliance

All subjects in this study will commence oral study drug administration under nursing supervision on C1D1.

Pexidartinib will be dispensed to subjects at the study visits indicated in the Schedule of Assessments (Section 1.3). The appropriate study personnel will document and maintain records of the 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.

6.5. Guidelines for Dose Modification

Reducing or interrupting the dose for toxicity may take place at any time during the study according to the guidelines in Table 6.2 and Table 6.3. Dose modification guidelines for hematologic and hematologic treatment-related TEAEs are based on severity. Dose interruption can be implemented at the discretion of the treating Investigator to manage intolerable or clinically significant toxicity. If 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 on 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 must 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 reduction 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, dose re-escalation is generally not allowed unless approved after discussion with the DS Medical Monitor or designee.

Table 6.2: Dose Modification Guidelines

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

The morning doses will be administered at 400 mg on C1D1 for the PK assessment.

Dose modification guidelines for treatment-emergent toxicities as well as guidelines for their management are presented in Table 6.3. 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 Medical Monitor or designee. Additional liver evaluation is presented in Table 6.4. 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 6.3: 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 6.4.
	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 6.4.

	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 6.4.
Increased ALP and 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 6.4.
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 6.4.
	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 6.4.
Adverse reactions or other laboratory abnormalities	Severe or intolerable	• Withhold until improvement or resolution to Grade 1 or subject's baseline. • Resume at a reduced dose upon improvement or resolution to Grade 1 or subject's baseline.

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

Table 6.4: 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.
Detailed medical history and physical examination seeking new abnormalities.	Evaluate any abnormalities found.

Full serological evaluation for hepatitis A, B, C, D, E (IgG and IgM), cytomegalovirus, Epstein-Barr virus, and herpes simplex virus. Check for autoimmune hepatitis with serological laboratory studies (eg, anti-nuclear antibody and anti-smooth muscle antibody).	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 days.	Contact Medical Monitor.
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 whenever the study drug is being held for liver function test abnormalities.	

AMA = anti-mitochondrial antibody; IgG = Immunoglobulin G; IgM = Immunoglobulin M; OTC = over-the-counter

6.6. Dosage Modification for Renal Impairment

The recommended dosage of pexidartinib for patients with mild to severe renal impairment (CL_{CR} 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.

6.7. Prior and Concomitant Medications

During the study, if the use of any concomitant treatment becomes necessary (eg, for treatment of an adverse event [AE]), the treatment must be recorded in 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 in the eCRF. Analgesic use and the analgesic regimen will be recorded.

Prohibited Therapies/Products

The following medications/therapies and products will be prohibited during the Treatment Period:

- Other investigational therapeutic agents
- Other products known to cause hepatotoxicity
- PPIs and P-CABs
  - As an alternative to a PPI or a P-CAB, 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.
- Strong CYP3A inducers, including St John's wort (see Section 10.3.3, a list of common CYP3A inhibitors and inducers)
- Moderate or strong CYP3A inhibitors, including grapefruit juice and seville orange juice, or Uridine 5'-diphospho-glucuronosyltransferase (UGT) inhibitors
  - If concomitant use with a moderate or strong CYP3A inhibitor or UGT inhibitor cannot be avoided, reduce the pexidartinib dose according to the recommendations in Table 6.5. 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 6.5: 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

BID = twice daily

- 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 up 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).

- Joint aspiration*

  *: Not to be prohibited from Protocol Version 4.0 onwards.

Permitted Therapies/Products

Subjects are permitted to receive prophylactic or supportive treatment as standard of care during the Treatment Period, per the Investigator's discretion and institutional guidelines.

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

7. STUDY DRUG DISCONTINUATION AND DISCONTINUATION FROM THE STUDY

7.1. Discontinuation of Study Drug

The primary reason for the permanent discontinuation of pexidartinib treatment administration must be recorded. Reasons for treatment discontinuation include:

- AE
- Progressive Disease (PD)
- Withdrawal by Subject (**to discontinue study drug**) NOTE: in this section this is only withdrawal for treatment with study drug and is NOT the same thing as a complete withdrawal from the study. Discuss with the subject that they will remain in the study (ie, continue with study visits and assessments, including LTFU).
- Investigator Decision
- Protocol Deviation
- Surgery
- Subject Noncompliance
- Pregnancy
- Study Termination by Sponsor
- Death
- Lost to Follow-up (see Section 7.3 for details on when a subject is considered Lost to Follow-up)
- Other

During the study, if a subject experiences radiological progression documented by central or local 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 Medical Monitor or designee to allow the subject to remain in the study.

After study drug is permanently discontinued for any reason other than death or lost to follow-up, the subject will be treated as clinically indicated by the Investigator or referring physician.

The Investigator must discuss with the subject that their decision to permanently discontinue the study drug means the subject still agrees to continue into the Follow-up Period for onsite or modified follow-up visits. Subjects will be followed at regularly scheduled intervals (see the Schedule of Assessments [Section 1.3]).

Procedures for Discontinuation from Study Drug

The subject should be instructed to contact the Investigator or study site staff before or at the time study drug is discontinued.

If a subject is discontinued from the study drug:

- The reason(s) for discontinuation and the last dose date should be documented in the subject's medical record and eCRF;
- Due to an AE, the Investigator will follow the subject until the AE has resolved or stabilized;
- The Investigator will notify DS and ensure that the procedures listed in the "post-treatment visit" column in the Schedule of Assessments (Section 1.3) are performed at 28 ± 7 days after the subject's last dose of the study drug and prior to initiating any new TGCT therapy, including surgery, whichever occurs first.
- LTFU evaluations will be performed to assess disease relapse or progression status as described in the Schedule of Assessments (Section 1.3).

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.

The Investigator will complete and report the observations as thoroughly as possible up to the date of discontinuation, including the date of last dose.

If a subject does not agree to continue to come to the study site, then a modified follow-up must be arranged to ensure the continued collection of endpoints and safety information. Options for modified follow-up are noted below.

Modified Follow-up Options for Subjects Who Discontinue the Study Drug and Do Not Agree to Study Visits

The following modified follow-up options can be offered to the subject who discontinue the study drug and does not agree to study visits at the study site.

- Study personnel contacting the subject by telephone (may be quarterly, bi-annually, annually, or only at EOS)
- Study personnel contacting an alternative person (eg, family member, spouse, partner, legal representative, physician, or other healthcare provider)
- Study personnel accessing and reviewing the subject's medical information from alternative sources (eg, doctor's notes, hospital records)

Dates of the modified follow-up contact(s) should be recorded. See Section 7.2 for definition of withdrawal by subject from the study (ie, withdrawal of consent).

7.2. Subject Withdrawal/Discontinuation from the Study

Subjects may discontinue from the study for any of the following reasons:

- Death

- Withdrawal by Subject (**from the study**) NOTE: this indicates that the subject withdraws consent and refuses to undergo any further study procedures or be followed for LTFU
- Lost to Follow-up (see Section 7.3 for details on when a subject is considered Lost to Follow-up)
- Study Termination by Sponsor
- Other

If the reason for study discontinuation is the death of the subject, the option for categorizing the primary cause of death is AE. If reason of death is unknown every effort should be made to obtain the primary cause of death. Only one AE will be recognized as the primary cause of death.

Only subjects who refuse all of the following methods of follow-up will be considered to have withdrawn consent from study participation (ie, from the interventional portion and follow-up):

- Attendance at study visits per protocol
- Study personnel contacting the subject by telephone
- Study personnel contacting an alternative person
- Study personnel accessing and reviewing the subject's medical information from alternative sources

If the subject refuses all of the above methods of follow-up, the Investigator should personally speak to the subject to ensure the subject understands all of the potential methods of follow-up. If the subject continues to refuse all potential methods of follow up, the Investigator will document this as a withdrawal of consent (from the interventional portion and follow-up).

Withdrawal Procedures

If a subject is withdrawn from both the interventional and follow-up portions of 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, date of last contact, and the reason for withdrawal;
- And disclosure of future information is also withdrawn, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent;
- The subject may request destruction of any samples taken and not tested, and the Investigator must document this in the site study records;
- Study site personnel may use local, regional, and national public records (in accordance with local law) to monitor vital status.

See the Schedule of Assessments (Section 1.3) for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.

7.3. Lost to Follow-up

Subjects will be considered lost to follow-up if he/she fails to return for 2 scheduled visits and is unable to be contacted by the study site staff. Before a subject is deemed lost to follow-up, the Investigator or designee will make every effort to regain contact with the subject (where possible, 3 telephone calls, texts, emails, and if necessary, a certified letter to the subject's last known mailing address or local equivalent methods). These contact attempts should be documented.

If direct contact with the subject is not possible the site must make every effort to collect disease relapse or progression status from public records (eg, obituaries, death certificates, etc.) in accordance with local laws.

8. STUDY PROCEDURES

See the Schedule of Assessments (Section 1.3). 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 must be performed within 28 days (Part 1) or 42 days (Part 2) before the first dose of the study drug, unless otherwise noted.

If 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.

8.1. Eligibility Assessment

Review the subject's demographics, medical and target disease history, vital signs, and results of tests (eg, physical examination, ECHO/MUGA, ECG, laboratory assessments) and compare against the eligibility criteria (Sections 5.1 and 5.2). If the subject is a screen failure, deactivate the subject in the IRT. See Section 5.3 for rescreening/subject replacement.

Informed Consent

Before a subject’s participation in the study, it is the Investigator’s responsibility to obtain freely given consent, in writing, from the subject after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study and before any protocol-specific procedures or any study drugs are administered. Subjects should be given the opportunity to ask questions and receive responses to their inquiries and should have adequate time to decide whether or not to participate in the study. The written ICF should be prepared in the local language(s) of the potential subject population. See Section 10.1.2 for additional details.

General Medical History and Baseline Conditions

Subject’s medical history (including TGCT treatment history and smoking history) will be obtained by the Investigator or a qualified designee.

Untoward medical occurrence (including clinically relevant laboratory values that are not symptoms of TGCT/vital signs that are out of range) that were diagnosed or known to exist prior to the first dose of study medication will be recorded on the General Medical History and Baseline Conditions eCRF, not the Adverse Event eCRF. Record the start date of any medical occurrence that started after the ICF was signed and is ongoing at the time of the first dose of pexidartinib on the General Medical History and Baseline Conditions eCRF.

Demographics

Review the subject’s demographics (including ethnicity and race) against the eligibility criteria.

8.2. Enrollment

After all screening procedures have been performed, the results of screening tests are available (ie, between the Screening visit and C1D1), and subjects are confirmed to continue to meet all eligibility criteria, the eligible subjects will be enrolled in the study to receive pexidartinib. If subjects do not meet the eligibility criteria on the day of enrollment, Investigators must discuss it with the Sponsor Clinical Leader or Scientist.

8.3. Efficacy Assessments

Radiographic Tumor Assessments

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.

No confirmation (ie, CR or PR at the subsequent MRI assessment) will be required for a CR or PR. CR and PR will define the 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-week treatment with respect to the primary efficacy endpoint is shown in Table 8.1.

To be considered a response, a tumor must meet the criteria for response and must show 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/non-not evaluable [non-NE]) at Week 25 will be considered a responder for the primary efficacy endpoint.

Table 8.1: 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 PD 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 the 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.

Tumor Imaging

Noncontrast MRI of the affected joint will be performed at the study visits indicated in the Schedule of Assessments (Section 1.3).

All MRI scans up to Protocol Version 3.0 will be centrally read, while MRI scans from Protocol Version 4.0 onwards will not be centrally read. Local evaluation of radiological response, 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 up to Protocol Version 3.0 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, the subject will be discontinued from the study unless the Investigator and the DS 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. While progression status will be assessed only by local read from Protocol Version 4.0 onwards. The details for MRI scan read 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.

Tumor Volume Score

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 multi-feature score (Rheumatoid Arthritis MRI Score), originally developed for rheumatoid arthritis[13] and whole-organ MRI score (WORMS), originally developed for osteoarthritis.[14] 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:

- CR: 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 (Study PLX108-01[10]). The tumor response status on this endpoint within 24-week treatment is determined in a way similar to that for the primary efficacy endpoint (Table 8.1). To minimize bias and reduce variability, MRIs for the primary 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.

Range of Motion Assessment

ROM 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 the American Medical Association disability criteria.[15] Measurements will be recorded in degrees. Details of the measurement procedure for each joint will be provided in the manual.

PROMIS Physical Function Scale

Subjects will complete the PROMIS Physical Function Scale for the indicated study visits in the Schedule of Assessments (Section 1.3). Physical function items relevant to the assessment of lower and upper limb function are to be selected from the PROMIS physical function item bank. 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.

Brief pain inventory Worst Pain Numeric rating scale Item

The BPI Worst Pain NRS item is a one-item self-administered questionnaire assessing the "worst" pain in the last 24 hours. The NRS for this item ranges from 0 ("no pain") to 10 ("pain as bad as you can imagine").

The five-level version of EuroQol five-dimensional questionnaire

Subjects will complete the five-level version of EuroQol five-dimensional questionnaire (EQ-5D-5L) for the indicated study visits in the Schedule of Assessments (Section 1.3).

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."

Surgical Assessment Questionnaire

The surgical assessment questionnaire (Section 10.7.1) will be completed by a qualified individual (eg, orthopaedic oncologist) to assess the surgical status of the subject at the Screening visit and at the time points shown in the Schedule of Assessments (Section 1.3).

Analgesic Use and Analgesic Regimen

Subjects will have a diary in which to record any analgesics, including nonsteroidal anti-inflammatory drugs and prescription analgesics, taken during the period before investigational product initiation and during the time period when the BPI Worst Pain is scheduled for completion. Subjects must have a stable prescribed analgesic regimen during the 2 weeks prior to the first dose of the study drug. During the study, whenever possible, the type and dose of

long-acting narcotic analgesic and non-narcotic analgesic should be kept stable while the dose of short-acting (or rescue) narcotic analgesic might be titrated as needed. Analgesic use will be quantified by multiplying the daily dose unit by the number of units taken, averaged by the number of days with available data.[16] For subjects who have changed narcotic type or if dosages have been changed in subjects concomitantly receiving different narcotic types, analgesic use will be calculated following equianalgesic conversion to morphine-equivalent doses.[17] Analgesic regimen, both prescription and OTC, will be collected in the eCRF in the same manner as other concomitant medications.

Photographic Documentation of Tumor Size Change

Photographic documentation will be collected to assess change in tumor size based on photographs if applicable.

Long-Term Follow-up Questionnaire

After completion of the EOS or early termination visit, the LTFU will be performed every 6 months by telephone contact. The questionnaire is provided in Section 10.7.2.

8.4. Safety Assessments

8.4.1. Adverse Event

Method to Detect Adverse Events

The definitions of an AE or serious adverse event (SAE) can be found in Section 10.4. AEs may be directly observed, reported spontaneously by the subject or by questioning the subject (or, when appropriate, by a caregiver, surrogate, or the subject's legally authorized representative) 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. The Investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following AEs that are serious, considered related to the study drug or study procedures, or that caused the subject to discontinue pexidartinib.

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

Time Period for Collecting Adverse Events, including Adverse Events of Special Interest and Serious Adverse Events

All SAEs occurring after the subject signs the ICF and up to 28 ± 7 days after the last dose of study medication (ie, the Follow-up Period), whether observed by the Investigator or reported by the subject, will be recorded on the Adverse Event eCRF. All SAEs will be followed until resolution, stabilization, the event is otherwise explained, or the subject is lost to follow-up.

All non-serious AEs occurring after the subject has signed the ICF until 28 ± 7 days after the last dose of study medication will be recorded on the Adverse Event eCRF.

Exacerbation of a pre-existing medical condition and symptom after the subject signs the ICF including increase in severity of the symptom will be recorded as an AE on the Adverse Event eCRF, unless it is a condition of TGCT.

Reporting Procedure for Investigators

All AEs (including adverse events of special interests [AESIs] and SAEs) will be reported in the Adverse Event eCRF. All AEs (serious and non-serious) must be reported with the Investigator's assessment of seriousness, severity, and causality to the pexidartinib.

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.

Disease-Specific Adverse Events and Serious Adverse Events

Disease progression/worsening of TGCT will **not** be recorded as an AE on the Adverse Event eCRF. However, events associated with disease progression, such as joint swelling, may be recorded as AEs.

Death due to disease progression should be recorded on the Death eCRF.

8.4.1.1. Serious Adverse Events Reporting

The following types of events should be reported by the Investigator in the electronic data capture (EDC) or on a Serious Adverse Event Report (SAVER) form within 24 hours of awareness:

- SAEs (Section 10.4.2)
- AESIs: Liver enzyme elevations and bilirubin elevation including hepatic events (both serious and non-serious) meeting the laboratory criteria of a potential Hy's Law criteria (as defined in Section 8.4.1.2)
- Overdose (Section 8.4.1.1.1)

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

If using EDC for SAE reporting: Complete the SAVER Form or the eCRF within 24 hours of awareness. In the event that the eCRF is unavailable, report SAEs by faxing or emailing the SAVER Form to Sponsor using the provided fax transmittal form and the appropriate fax number provided for your country or email address. Once EDC becomes available, please enter SAEs

reported on the SAVER Form into the eCRF as soon as possible. Please refer to the eCRF Completion Guide for additional instructions.

Call the local SAE Hotline (see Study Site Manual) or your study monitor for any questions on SAE reporting.

See Section 8.4.1 for details on the time period for collecting SAEs.

Reporting Requirement to Sites and Regulatory Authorities

The Sponsor or CRO will inform Investigators and regulatory authorities of any suspected unexpected serious adverse reactions (SUSARs) occurring in study sites or other studies of pexidartinib, as appropriate per institutional and/or local reporting requirements.

The Sponsor and/or CRO will comply with any additional local safety reporting requirements. The Investigator will assess if an AE is to be considered "unexpected" based on the "Reference Safety Information" section in the current IB.[10]

Follow-up for Adverse Events and Serious Adverse Events

The Investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

Urgent safety queries must be followed up and addressed promptly. The Investigator will submit any updated SAE data to the CRO or sponsor within 24 hours of receipt of the information. Follow-up information and response to non-urgent safety queries should be combined for reporting to provide the most complete data possible within each follow-up report.

8.4.1.1.1. Overdose

An overdose is defined as the accidental or intentional administration of any dose of a product 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 will be reported via SAVER/overdose form or eCRF.

An "excessive and medically important" overdose includes any overdose in which either an SAE, a non-serious AE, or no AE occurs and is considered by the Investigator as clinically relevant, ie, poses an actual or potential risk to the subject.

8.4.1.2. Adverse Events of Special Interest

The following are considered to be AESIs.

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 gamma-glutamyl transpeptidase (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

  Hepatic events (both serious and non-serious) which meet the potential Hy's Law criteria defined as an elevated (ALT and/or AST) ≥3 × ULN and an elevated total bilirubin >2 × ULN, regardless if it is due to disease progression per Investigator assessment, that may occur at different time points during the study conduct, should always be reported to the Sponsor.[18]

These events must be reported either by a SAVER form or eCRF, with the investigator's assessment of seriousness, severity, causality, and a detailed narrative. These events should be reported within 24 hours of the investigator's awareness of the event regardless of seriousness. A targeted questionnaire will be available as an eCRF to collect relevant additional information for these potential cases.

If the subject meets the criteria described in Table 6.3 due to liver enzyme abnormalities, the subject will have additional clinical and laboratory evaluations as described in Table 6.4 to determine the nature and severity of the potential liver injury.

8.4.2. Pregnancy

Sponsor must be notified of any female subject or partner of a male subject who becomes pregnant while receiving or within 90 days of discontinuing pexidartinib. 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. If a pregnancy is reported, the Investigator should inform the Sponsor within 24 hours of learning of the pregnancy.

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 partner of a male subject using the Exposure In Utero (EIU) Reporting form. Please contact your study monitor to receive the EIU Reporting Form upon learning of a pregnancy. The Investigator should make every effort to follow the female subject or partner of a male subject (upon obtaining written consent from partner) until completion of the pregnancy and complete the EIU Reporting Form with complete pregnancy outcome information, including normal delivery and induced abortion. Any adverse pregnancy outcome, either serious or non-serious, should be reported in accordance with study procedures. If the outcome of the pregnancy meets the criteria for immediate classification as an SAE (ie, post-partum complications, spontaneous or induced abortion, stillbirth, neonatal death, or congenital anomaly, including that in an aborted fetus), the Investigator should follow the procedures for reporting SAEs.

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 Assessments (Section 1.3).

For postmenopausal subjects (no childbearing potential, as indicated by a lapse 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.

8.4.3. Dose-Limiting Toxicities

Definition of Dose-Limiting Toxicity

A DLT is defined as any TEAE not attributable to disease or disease-related processes that occurs during the DLT-evaluation period Day 1 to Day 28 in Cycle 1 of Part 1 and is Grade 3 or above, according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 5.0, with the exceptions defined in Table 8.2 below.

Table 8.2: Dose-Limiting Toxicities

Category	Definition
Hematological toxicities	· Grade 4 decreased neutrophil count lasting >7 days or a decreased neutrophil count that requires standard therapies, such as colony stimulating factor · Grade ≥3 febrile neutropenia · Grade 4 anemia · Grade ≥3 anemia associated with transfusion · Grade 4 decreased platelet count · Grade ≥3 decreased platelet count lasting >7 days · Grade ≥3 decreased platelet count with clinically relevant hemorrhage · Grade ≥3 decreased platelet count associated with transfusion · Grade 4 decreased lymphocyte count lasting ≥14 days
Hepatic organ toxicities	· Grade 4 increased serum AST or serum ALT · AST or ALT ≥ × 3 ULN, if accompanied by ≥2 × ULN in total bilirubin · AST or ALT > × 5 ULN lasting >14 days
Non-hematological, non-hepatic major organ toxicities	· Symptomatic congestive heart failure · LVEF decline to <40% or >20% drop from baseline
Other	Inability to complete at least 75% of the prescribed doses in Cycle 1 as a result of Grade ≥2 AE not attributed to disease

ALT = alanine aminotransferase; AST = aspartate aminotransferase; LVEF = left ventricular ejection fraction; ULN = upper limit of normal

Toxicities will be graded according to the NCI-CTCAE version 5.0. If multiple toxicities are encountered, then DLT assessment will be based on the most severe toxicity experienced. With regard to other toxicities that impact the conduct of the scheduled study treatment whether they

are regarded as DLT will be determined based on consultation between the Investigator and Sponsor.

The following TEAEs are NOT considered DLTs:

- Grade 3 fatigue lasting <7 days;
- Grade 3 nausea, vomiting, diarrhea, or anorexia that has resolved to Grade ≤2 within 3 days;
- Isolated laboratory findings not associated with signs or symptoms including Grade 3/4 hyperuricemia, increased serum amylase, increased lipase, and Grade 3 hyponatremia lasting <72 hours which has increased from Grade 1 at baseline;
- Grade 3 decreased lymphocyte count.

Study drug must be withheld for any subject who experiences a DLT but may resume at the same or lower dose level, after the toxicity has resolved or improved and following discussion between the Investigator(s) and the Sponsor based on Table 6.3.

Premedication, (any treatment administered prior to study treatment administration to avoid TEAEs) is prohibited during the DLT evaluation period.

Unscheduled visits should include all of the protocol scheduled procedures for that particular cycle/week, to ensure safety parameters are continuous throughout the subject's study participation. These visits should include but are not limited to the following assessments: confirming medical history conditions that were ongoing at the previous visit are still ongoing, physical examinations, vital signs, weight, clinical laboratories, and AEs. Visits occurring during the study weeks where drug is held will be recorded as additional week(s) of the concurrent cycle.

Subjects missing more than 25% of scheduled doses in the DLT period for reasons not related to AEs (eg, noncompliance) will not be evaluable for DLT.

8.4.4. Clinical Laboratory Evaluations

Clinical laboratory evaluations will be performed at the local laboratory at the study visits indicated in the Schedule of Assessments (Section 1.3). For clinical laboratory parameters, the reference range of the institution that performs the measurement will be used. Refer to Section 10.2 for the complete list of laboratory parameters.

New or worsened clinically relevant abnormalities should be recorded as AEs on the Adverse Event eCRF.

Others

A serum sample must be collected for anti-mitochondrial antibody (AMA) at Screening and when severe hepatotoxicity is observed (Section 6.5).

8.4.5. Other Safety

Physical Examinations, Weight, and Height

The examination will be performed by a qualified individual such as the Investigator at the study visits indicated in the Schedule of Assessments (Section 1.3).

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.

Weight will be measured at the study visits mentioned in the Schedule of Assessments (Section 1.3). Height will be measured at the Screenings visit only.

Vital Signs

Vital signs, including systolic/diastolic blood pressures, pulse rate and temperature will be measured in accordance with the institutional standards and generally must be performed before any invasive procedures, eg, blood sampling. Vital signs will be measured at the study visits mentioned in the Schedule of Assessments (Section 1.3).

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

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

Electrocardiograms

A standard 12-lead ECG will be obtained at the study visits indicated in the Schedule of Assessments (Section 1.3).

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 findings must be recorded in 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 the study drug; instead, they must be told to bring their bottle of the study drug to the site and take the morning dose upon instruction by the site staff.

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

Multi-gated Acquisition Scan or Echocardiogram

MUGA/ECHO must be performed as per the Schedule of Assessments (Section 1.3). Subjects must have a LVEF ≥50% to be eligible for the study. In this protocol, "ECHO scan" and

"MUGA scan" will be used interchangeably. The choice of whether to perform ECHO or MUGA scan will be based on the preference of the investigator, but the platforms should not be switched during the course of a subject's study participation. Clinically important findings, including LVEF, will be recorded in the appropriate eCRF.

8.5. Pharmacokinetic (PK) Assessment(s)

Blood samples for PK analyses will be obtained at the time points shown in Table 8.3.

Plasma concentration-time profiles of pexidartinib and ZAAD-1006a will be established based on the blood PK samples collected on C1D1, C1D15 intensively and on C2D1, C3D1, C5D1 sparsely both in Part 1 and Part 2.

Plasma concentrations of pexidartinib and ZAAD-1006a will be measured using validated assays at the bioanalytical laboratory.

Table 8.3: Schedule of PK Sample Collection

Visit	Schedule
Week 1 C1D1 - C1D2	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) 8 h postdose (± 20 min) 24 hours post-dose (within 3 hours pre-dose on C1D2)
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)
Week 5 C2D1	Predose Random postdose
Week 9 C3D1	Predose Random postdose
Week 17 C5D1	Predose Random postdose

C = Cycle; D = Day; h = hour; min = minutes

Plasma-concentration data of pexidartinib and ZAAD-1006a on C1D1 and C1D15 (Week 3) will be analyzed for the PK analysis set using standard non-compartmental methods. The following PK parameters will be calculated.

C1D1: Cmax, Tmax, AUC6h, AUC24h, AUClast, AUCinf*, Kel*, t1/2*, CL/F*, Vz/F*

C1D15: Cmax, Tmax, AUC6h, Ctrough AR

*: To be calculated only if possible.

The PK parameters of pexidartinib will be listed for each subject and summarized using descriptive statistics.

The actual times of study drug administration and the exact time of blood sampling for PK analysis must be recorded in the eCRF.

Detailed instructions for the collection, handling, and shipping of samples are outlined in the Study Laboratory Manual.

Population Pharmacokinetic Analysis and Exposure-Response Analysis

Plasma-concentration data from these samples will be analyzed applying a population pharmacokinetic (PopPK) approach using nonlinear mixed effects modeling by pooling with data of other studies to assess and characterize the inter- and intra-subject variability of PK and to identify significant covariates. These analyses will be summarized in a separate report.

Bayesian individual exposures of pexidartinib from the PopPK analysis will be used to explore the relationship between exposure metrics and biomarkers and safety and efficacy endpoints. The results of these analyses will be reported separately from the Clinical Study Report (CSR).

8.6. Biomarker Assessments

8.6.1. Biomarker Analysis for Pharmacodynamics*

- CSF-1 and IL-34 concentrations will be measured by enzyme-linked immunosorbent assay (ELISA) in plasma samples collected pre-, on and at end of treatment.
- Profile of immune cells will be evaluated with flow cytometry using blood samples collected pre-, on and at end of treatment.
- Profile of immune cells will be evaluated with immunohistochemistry using tumor biopsies collected pre- (mandatory), on and at end of treatment (optional). For pre-treatment biopsies, archived tumor samples will be acceptable instead of freshly collected biopsies.

*: Sample collection will not be performed from Protocol Version 4.0 onwards.

8.6.2. Biomarker Analysis for Subject Characterization*

- The status of CSF-1 rearrangements pre-treatment will be evaluated with either fluorescence in situ hybridization (FISH), DNA sequencing or RNA sequencing of tumor samples.
- The profile of tumor-infiltrating immune cells will be evaluated with immunohistochemistry and/or flow cytometry of biopsied tissue and blood samples collected pre-treatment.

- The profile of drug-metabolizing enzyme and transporter gene mutations will be evaluated with Thermo Fisher Pharmacoscan™ assay in blood samples collected pre-treatment.
- The status of CSF1R gene mutation will be evaluated with next generation sequencing (NGS) in blood samples collected pre-treatment.

*: Sample collection will not be performed from Protocol Version 4.0 onwards.

The results of these biomarker analyses will be reported separately from the CSR.

8.6.3. Biomarker Analysis Potential for In Vitro Diagnostics / Companion Diagnostics

Not applicable.

8.6.4. Additional Biomarker Assessments

The remaining samples of each subject who consented will be stored for a maximum of 15 years after the finalization of the CSR for this protocol.

Biopsied tissue sample banking for future biomarker analyses, which may include comprehensive gene mutation and gene expression profiling with NGS and /or RNA-sequencing.

8.6.5. Pharmacogenomic (Inherited Genetic) Analysis

A single blood sample for pharmacogenetic analysis will be collected pre-treatment from each randomized subject. Detailed instructions for the collection, handling, and shipping of samples are outlined in the Study Laboratory Manual. The pharmacogenetic analysis is as follows; 1) Profile of drug-metabolizing enzyme and transporter gene mutations will be evaluated with Thermo Fisher Pharmacoscan™ assay in blood samples collected pre-treatment. 2) Status of CSF1R gene mutation will be evaluated with NGS in blood samples collected pre-treatment, as described in Section 8.6.2.

Genetic analyses will not be performed on whole blood samples collected for PK or safety assessments unless consent for this was obtained. Subject confidentiality will be maintained. If the subjects agree, the remaining DNA will be stored, as outlined in Section 8.6.5.1 to perform pharmacogenetic analysis in the future, otherwise all remaining DNA samples will be destroyed.

8.6.5.1. Banking of Specimens for Inherited Genetic Analysis

Procedures for the long-term preservation (banking) of blood and/or DNA specimens extracted from subjects' blood samples for each subject who consented are described in the Study Laboratory Manual.

The banked samples may be analyzed for genes involved in absorption, distribution, metabolism, elimination, safety, and efficacy of pexidartinib. Additionally, samples may be analyzed for genes involved in pexidartinib-related signaling pathways, or to examine diseases or physiologic processes related to pexidartnib. This information may be useful in increasing the knowledge of differences among individuals in the way they respond to the study drug, as well as helping in the development of new drugs or improvement of existing drugs.

Storage and Disposal of Specimens

Banked DNA samples will be stored for a maximum of 15 years after the finalization of the CSR for this protocol. These specimens will be kept for pharmacogenetic analysis in case new genomic or genetic information is obtained in the future regarding the response (PK or pharmacodynamic [Pdy]) to pexidartinib or in case serious adverse drug reactions are noted in a clinical study and pharmacogenetic analysis is to be conducted for investigation into the cause.

During the storage period, the samples will be coded with labels having no personal information and will not be immortalized or sold to anyone. Subjects will have the right to withdraw consent and have their sample destroyed at any time. However, the data will not be discarded if analysis has been completed before the subject withdraws consent.

Disclosure of the Results of Future Pharmacogenetic Analysis

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

9. STATISTICAL CONSIDERATIONS

9.1. 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. The final analysis of the study will occur after all subjects have discontinued the study. Data collected beyond the primary analysis cut-off time point will be presented as appropriate in a CSR addendum.

The data cutoff for safety and PK analysis in Part 1 will occur after all subjects have received pexidartinib and have either completed the minimum safety evaluation requirements over the DLT evaluation period (28 days) or have experienced a DLT during the DLT evaluation period.

Data analysis will also be conducted separately by Part 1 and Part 2. The pooled analysis may be planned in the Statistical Analysis Plan (SAP).

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 non-missing value of a variable taken before the first dose of the 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 and secondary efficacy endpoints, with the exception of duration of response, the 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.

No formal interim analysis is planned in Part 1 or Part 2.

For all analysis, the Part 1 data at the end of Part 1 will be used.

The all analysis including the efficacy analysis of the subjects in Part 1 was originally planned to be performed at the end of Part 2. However, the sponsor decided not to proceed with Part 2. Depending on this decision, the Part 1 data will be analyzed at the end of Part 1, and the efficacy analysis will be performed as the exploratory analysis.

9.2. Statistical Hypothesis

In Part 1:

The following is the hypothesis in Part 1, but there is no specific statistical criteria to evaluate this hypothesis:

Treatment with pexidartinib (800 mg/day [400 mg BID]) will be well tolerated in Japanese TGCT patients.

In Part 2:

The following is the hypothesis in Part 2, but there is no specific statistical criteria to evaluate this hypothesis:

Treatment with pexidartinib (800 mg/day [400 mg BID]) will present an acceptable and manageable safety profile in Japanese TGCT patients.

There is no formal statistical hypothesis.

In June 2024, the sponsor decided not to proceed with Part 2. Therefore, the statistical hypothesis for Part 2 will not be confirmed.

9.3. Sample Size Determination

In Part 1:

Sample size was determined based on practical considerations and no formal statistical assessment has been performed. The total sample size is 3 to 6 DLT evaluated subjects.

In Part 2:

15 subjects.

The assumed ORR of the primary endpoint is 37.7% based on the ORR for pexidartinib in the ENLIVEN study. Based on the use of a one-side, exact binomial test of a proportion against the null hypothesis of 5% at the one-sided alpha = 0.05 level of significance, a sample size of 13 subjects provides more than 90% power to detect this magnitude of difference.

The sample size calculation was performed in SAS version 9.4.

9.4. Population for Analysis Sets

Analysis Sets

- The **Full Analysis Set (FAS)** will include all subjects who received at least 1 dose of pexidartinib.
- The **Safety Analysis Set** will include all subjects who received at least 1 dose of pexidartinib. The safety analysis set and FAS are identical in this study.
- The **DLT Evaluable Set** will include all subjects who received at least 1 dose of pexidartinib and experienced a DLT prior to Day 28 of Cycle 1 or completed the DLT evaluation period (Day 1 of Cycle 1 to Day 28 of Cycle 1).
- The **PK Analysis Set** will include all subjects who received at least 1 dose of pexidartinib and had measurable plasma concentrations of pexidartinib.
- The **Biomarker Analysis Set** will include all subjects who received at least 1 dose of pexidartinib and had Pdy biomarker evaluation.

The DLT evaluable set will be used for analysis in Part 1. Other analysis sets will be used both in Part 1 and Part 2.

9.5. Statistical Analysis

The SAP will be developed and finalized before database lock and will describe the subject populations to be included in the analyses, and procedures for accounting for missing, unused, and spurious data. This section is a summary of the planned statistical analyses of the primary, secondary and exploratory endpoints.

9.5.1. Efficacy Analyses

Table 3.1 lists the primary and secondary efficacy endpoints and their corresponding definitions of all endpoints. Additional details for the analysis is noted in the following sections.

In June 2024, the sponsor decided not to proceed with Part 2. Therefore, the primary efficacy analysis and the secondary efficacy analysis will be performed as the exploratory efficacy analysis using Part 1 data.

9.5.1.1. Primary Efficacy Analyses

The primary efficacy analysis will be based on the data from FAS in Part 2.

The primary efficacy endpoint is shown in Table 8.1. It will be the proportion of subjects who achieved a CR or PR (ORR) based on RECIST 1.1 by centrally reviewed MRI scan. No confirmation (ie, CR or PR at the subsequent MRI assessment) will be required for a CR or PR. The estimate of the proportion and two-sided 95% CI based on the Clopper-Pearson method will be provided.

Additional subgroup analyses to assess the homogeneity of the treatment effect based on demographic and baseline disease characteristics may be performed; details about the subgroups to be included will be provided in the study SAP.

9.5.1.2. Secondary Efficacy Analyses

The secondary efficacy endpoints will be provided in Part 2:

- Proportion of TVS responders who achieve a CR or PR at Week 25 based on TVS by centrally reviewed MRI scan
- Mean change from baseline in ROM of the affected joint, relative to a reference standard for the same joint at Week 25
- Mean change from baseline in the PROMIS Physical Function Scale at Week 25
- Proportion of BPI responders based on the BPI Worst Pain NRS item and analgesic use by BPI-30 definition (subject who (i) experienced a decrease of at least 30% in the mean BPI Worst Pain NRS item and (ii) did not experience a 30% or greater increase in narcotic analgesic use when compared to baseline)
- Best overall response (BOR) based on RECIST 1.1 by centrally reviewed MRI scan
- BOR based on TVS by centrally reviewed MRI scan
- Duration of response (DoR) based on RECIST 1.1 by centrally reviewed MRI scan

- DoR based on TVS by centrally reviewed MRI scan

A brief description of each analysis is provided below:

- An estimate of the proportion of TVS responders and BPI responders and the two-sided 95% CI based on the Clopper-Pearson method will be calculated. Subjects who do not provide data for each endpoint will be considered to be non-responders.
- Change from baseline in ROM and PROMIS will also be summarized with point estimates and 95% CIs.
- The percentage and 95% CI will be provided for the BOR
- DoR will also be analyzed as a secondary endpoint and will be summarized only for responders based on RECIST 1.1 and TVS. For subjects who do not have radiological progression, the duration of response will be censored. Subjects not known to have experienced an event at the time of data cut-off will be censored at the date of the last tumor assessment before the cut-off date. The SAP includes additional censoring rules. The Kaplan-Meier product limit method will be used to compute the estimate and 95% CI of the median and 25th and 75th percentiles.

9.5.1.3. Exploratory Analyses

The exploratory efficacy endpoints will be provided in Part 2:

- Proportion of subjects who achieve a CR or PR (ORR) at Week 25 based on RECIST 1.1 by locally reviewed MRI scan.
- Proportion of subjects who achieve a CR or PR (ORR) at Week 25 based on modified RECIST 1.1- sum of the short-axis dimension (SSD) by centrally reviewed MRI scan.
- Mean change from baseline score in the EQ-5D-5L at Week 25
- BOR based on RECIST 1.1 by locally reviewed MRI scan
- DoR based on RECIST 1.1 by locally reviewed MRI scan
- DoR based on modified RECIST 1.1-SSD by centrally reviewed MRI scan

A brief description of each analysis is provided below:

- An estimate of the proportion responders based on (i) RECIST 1.1 by local and (ii) modified RECIST 1.1-SSD by central evaluation and the two-sided 95% CI based on the Clopper-Pearson method will be calculated. Subjects who do not provide data for the endpoint will be considered to be non-responders.
- Change from baseline in EQ-5D-5L will also be summarized with point estimates and 95% CIs.
- The percentage and 95% CI will be provided for BOR in the order of CR, PR, SD, PD, and NE.
- DoR will also be analyzed as a secondary endpoint and will be summarized for responders based on (i) RECIST 1.1 by local and (ii) modified RECIST 1.1-SSD by central evaluation. For subjects who do not have radiological progression, the

duration of response will be censored. Subjects not known to have experienced an event at the time of the data cut-off will be censored at the date of the last tumor assessment before the cut-off date. The SAP includes additional censoring rules. The Kaplan-Meier product limit method will be used to compute the estimate and 95% CI of the median and the 25th and 75th percentiles.

Exploratory efficacy analyses will also be performed in Part 1.

9.5.1.4. Multiplicity Adjustment

Not applicable

9.5.2. Safety Analyses

Safety analyses will be performed using the Safety Analysis Set and subjects will be analyzed according to their actual treatment received in each Part except for DLT analyses.

Safety analyses in general will be descriptive and will be presented in tabular format with the appropriate summary statistics.

Dose-limiting Toxicities

The number of DLTs identified among the DLT-evaluable subjects in the DLT Evaluable Set will be listed and summarized.

Adverse Events

TEAEs are defined as new AEs or pre-existing conditions that worsen in CTCAE grade after the first dose of study drug and up to 28 day after the last dose of study drug. AEs collected after 28 days after the last dose of study drug will not be considered TEAEs unless they are treatment-related. AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) dictionary. An AE will be assigned to the study period in which it started, even if it resolved in a subsequent period. The number and percentage of subjects reporting TEAEs will be calculated overall, by system organ class, and by preferred term.

TEAEs will be further summarized by CTCAE grade and relationship to study drug. Similarly, the number and percentage of subjects reporting treatment-emergent SAEs and related treatment-emergent SAEs will be tabulated, treatment-emergent AESIs, and TEAEs associated with discontinuation of study drug.

A by-subject AE (including treatment-emergent) data listing including but not limited to verbatim term, preferred term, system organ class, CTCAE grade, and relationship to study drug will be provided. Deaths, other SAEs, AESIs, and AEs associated with study drug discontinuation, will be listed.

Clinical Laboratory Evaluation

Descriptive statistics will be provided for the clinical laboratory results by scheduled time of evaluation as well as for the change from baseline. The baseline value is defined as the last non-missing value before the initial administration of study drug. 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.

Additionally, for ALT, AST, total bilirubin, direct bilirubin, and ALP, the number and percentage of subjects who meet the criteria specified in the FDA Drug-Induced Liver Injury guideline[18] will be tabulated and evaluation of the drug-induced serious hepatotoxicity plot will also be provided.

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 two-way frequency tabulation for baseline and the worst post-treatment value according to the CTCAE grade, will be provided for clinical laboratory tests. A listing of abnormal clinical laboratory test results deemed of clinical significance or of Grade 3 or 4 will be generated.

Electrocardiogram

Descriptive statistics will be provided for the ECG measurements by scheduled time of evaluation, as well as for the change from baseline. The baseline value is defined as the last non-missing value before the initial administration of study drug. In addition, the number and percentage of subjects with ECG interval values meeting the criteria will be tabulated (eg, corrected QT interval [QTc] ≤450 ms, >450 to ≤480 ms, >480 ms to ≤500 ms, and >500 ms).

A listing of ECG data will be generated.

Vital Signs and Weight

Descriptive statistics will be provided for the vital signs measurements and weight by scheduled time of evaluation, as well as for the change from baseline. The baseline value is defined as the last non-missing value before the initial administration of study treatment. A listing of vital sign and weight data will be generated.

Other

Listings of all other safety endpoints (eg, ECHO/MUGA) will be generated.

9.5.3. HEOR Analysis

Not applicable

9.5.4. Other Analyses

The following other analyses are planned in this study.

Pharmacokinetics

Pharmacokinetics analyses will be performed using the PK Analysis Set. Plasma concentrations for pexidartinib and ZAAD-1006a will be listed, plotted, and summarized using descriptive statistics for each study day, dose, and time points. Pharmacokinetic parameters will be listed and summarized using descriptive statistics. These may include PopPK and PK/PD modeling and/or exposure-response analyses in a separate report, to characterize the relationship between exposure and PD endpoints and clinical outcomes.

Pharmacodynamics / Biomarkers

Pdy and biomarker analyses will be performed on the Biomarker analysis set.

Concerning pexidartinib-related biomarkers, for categorical data, frequency tables at each time point, and shift tables showing changes from before the start of treatment with pexidartinib will be prepared; for quantitative data, summary statistics of measured values and changes from pre-treatment will be calculated at each time point, and the time courses will be depicted in figures.

9.6. Interim Analyses

Not applicable.

10. APPENDICES - SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Appendix 1 Regulatory and Ethical Considerations

10.1.1. Regulatory Compliance

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

Changes in the conduct of the study or planned analysis will be documented in a protocol amendment and/or the SAP. Written approval of all protocol amendments and changes to any of the above listed documents must be obtained from the IRB or EC.

The Investigator should notify the IRB or EC of deviations from the protocol or SAEs occurring at the study site and other AE reports received from the Sponsor/CRO, in accordance with local procedures.

Compliance Statement, Ethics, and Regulatory Compliance

This study will be conducted in compliance with the protocol, the ethical principles that have their origin in the Declaration of Helsinki, the International Council for Harmonisation (ICH) consolidated Guideline E6 for Good Clinical Practice (GCP) (CPMP/ICH/135/95), and applicable regulatory requirement(s) including the following:

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

In addition, the Investigator will inform the Sponsor in writing within 24 hours 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.

Supply of New Information Affecting the Conduct of the Study

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

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

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

10.1.2. Informed Consent

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

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

If the subject cannot read, then according to ICH GCP Guideline, Section 4.8.9, an impartial witness should be present during the entire informed consent discussion. This witness should sign the ICF after the subject has consented to their participation. 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.

A separate special consent for inherited genetic analysis will be obtained from subjects in accordance with health authorities in their particular region/country.

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

10.1.3. Subject Confidentiality

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

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

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

10.1.4. Data Integrity and Quality Assurance

Monitoring and Inspections

The 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, eCRFs, source data, and other pertinent documents).

The verification of adherence to the protocol; completeness, accuracy, and consistency of the data; and adherence to ICH GCP and local regulations on the conduct of clinical research will be accomplished through a combination of onsite visits by the monitor and review of study data remotely. The frequency of 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 medical records and other study-related records needed to verify the entries on the eCRFs. Detailed information is provided in the monitoring plan.

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

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

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

Data Collection

An eCRF must be completed for each subject who signs an ICF and undergoes any screening procedure. If a subject is not treated, the reason must be recorded on the eCRF. All data collected during the study will be recorded in this individual, subject-specific eCRF. Instructions will be provided for the completion of the eCRF and any corrections made will be automatically documented via an "audit trail."

The eCRF should be kept current to enable the study monitor to review the subject's status throughout the course of the study. Upon completion of the subject's eCRF, it will be reviewed and signed off by the Investigator via the EDC system's electronic signature. This signature will indicate that the Investigator inspected or reviewed the data in the subject-specific eCRF, the data queries, and the site notifications and agrees with the eCRF content.

Data Management

Each subject will be identified in the database by a unique SID.

To ensure the quality of clinical data across all subjects and study sites, a DS/CRO Clinical and Data Management review will be performed on subject data according to specifications developed by the Sponsor. Data will be vetted both electronically by programmed data rules within the application and manually. 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 will be reconciled to the clinical database.

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

All concomitant medications and prior therapies will be coded using the World Health Organization Drug Reference (WHODRUG) Dictionary.

10.1.5. Committees

Safety Monitoring Committee

The SMC will be established for the purpose of assessing safety and tolerability of the subjects. The SMC meetings will be held after a certain number of the enrolled subjects in Part 1 have completed the DLT evaluation period. Ad hoc meetings will be held to discuss subject safety and DLT determination as needed.

The SMC will evaluate progress of the study, assess safety and other relevant information, and then make recommendations on study continuation or discontinuation. The SMC members may include the Sponsor or external medical experts, the Sponsor's clinical leader, and Investigators of study sites. Detailed procedures of the SMC will be specified in the SMC Charter.

Hepatic Adjudication Committee

An external hepatic adjudication committee (HEAC) will be used for evaluating important hepatic AEs. Details on the membership, responsibilities, and working procedures of the external HEAC will be described in a 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.

10.1.6. Study Documentation and Storage

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

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

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

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

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

Electronic CRF 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, IEC/IRB correspondence and approvals, approved and signed ICFs, Investigator's Agreement, clinical supplies receipts, distribution and return records), and other Sponsor correspondence pertaining to the study must be kept in appropriate study files at the study site (site specific 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 local laws or regulations or study site policy. Prior to transfer or destruction of these records, the Sponsor must be notified in writing and be given the opportunity to provide further instruction.

Record Keeping

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

- Subject files containing completed eCRFs, ICFs, and supporting 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 independent IRB/EC and the Sponsor.
- Records related to the study drug(s) including acknowledgment of receipt at study site, accountability records and final reconciliation and applicable correspondence.

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

All 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 laws or 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.

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

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

10.1.7. Finances

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

Reimbursement, Indemnity, and Insurance

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

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

10.1.8. Publication, Public Disclosure Policy, and Data Sharing

The Sponsor is committed to meeting the highest standards of publication and public disclosure of information arising from clinical studies sponsored by the company. The Sponsor will comply with US, EU, and Japanese policies for public disclosure of the clinical study protocol and clinical study results, and for sharing of clinical study data. The Sponsor will 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 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 disclosures) based on data generated in this study must be reviewed and approved in writing by the Sponsor prior to submission.

The data from this study may be shared with or used by third parties, including commercial partners.

10.1.9. Protocol Deviations

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

A deviation to any protocol procedure or waiver to any stated criteria will not be allowed in this study except where necessary to eliminate immediate hazard(s) to the subject.

The Sponsor must be notified in writing of all intended or unintended deviations to the protocol (eg, inclusion/exclusion criteria, dosing, missed study visits) within 24 hours or in accordance with the clinical study agreement between the parties.

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 study drug, data should be collected for safety purposes.

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

10.1.10. Study and Site Closure

The Sponsor reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the Sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The Investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the Sponsor or Investigator may include but are not limited to:

- Failure of the Investigator to comply with the protocol, the requirements of the IEC/IRB or local health authorities, the Sponsor's procedures, or GCP guidelines
- Inadequate recruitment of subjects by the Investigator
- Discontinuation of further study intervention development

10.2. Appendix 2: Local Laboratory

The clinical laboratory tests listed in Table 10.1 are to be performed in this study.

Table 10.1: Clinical Laboratory Tests

Test	Analytes	
Blood Chemistry	albumin blood urea nitrogen (BUN)/urea calcium (Ca) chloride (Cl) creatinine clearance (CL_{CR})/creatinine cholesterol (total)* glucose* HCO_3^-** lactate dehydrogenase	lipoprotein, high density (HDL)* lipoprotein, low density (LDL)* phosphorus potassium (K) protein (total) sodium (Na) triglycerides* uric acid
	<Liver Function Tests> alanine aminotransferase (ALT) alkaline phosphatase (ALP) aspartate aminotransferase (AST)	 bilirubin (total) bilirubin (direct) gamma-glutamyl transaminase (GGT)
Hematology	hemoglobin hematocrit platelet count	red blood cell (RBC) count white blood cell (WBC) count with differential
Coagulation	prothrombin time (PT) prothrombin time (PT)- international normalized ratio (INR) activated partial thromboplastin time (aPTT)	
Urinalysis (dipstick and microscopic analysis)	glucose/sugar hemoglobin/blood ketones/acetone nitrites pH	protein/albumin sediments: bacteria, casts, crystals, epithelial cells, RBCs, WBCs
Hormone	<Females> estradiol follicle stimulating hormone (FSH) luteinizing hormone (LH) progesterone	<Males> FSH LH testosterone
Hepatitis Panel	hepatitis B virus surface antigen test hepatitis B virus core antibody test hepatitis B virus surface antibody test hepatitis B virus DNA (only subjects who are on the treatment with other chemotherapy or immunosuppressive therapy) hepatitis C virus antibody test	
Others	anti-mitochondrial antibody	

* Fasting is recommended but not required.
** HCO_3^- concentration calculated from pH and pCO_2 measured with blood gas analyzers, using the Henderson-Hasselbalch equation, is acceptable as an alternative.

10.3. Appendix 3: Reference Standards

10.3.1. Cockcroft-Gault Equation

The estimated CL_{CR} (mL/min) will be calculated using the Cockcroft-Gault equation based on [actual/ideal] weight in kilograms (1 kilogram = 2.2 pounds):[19]

Conventional – serum creatinine in mg/dL:

Male:

$$CL_{CR}\ (mL/min) = \frac{[140 - age\ (in\ years)] \times weight\ (in\ kg)}{serum\ creatinine\ (in\ mg/dL) \times 72}$$

Female:

$$CL_{CR}\ (mL/min) = \frac{[140 - age\ (in\ years)] \times weight\ (in\ kg)}{serum\ creatinine\ (in\ mg/dL) \times 72} \times 0.85$$

International System of Units (SI) – serum creatinine in µmol/L:

Male:

$$CL_{CR}\ (mL/min) = \frac{[140 - age\ (in\ years)] \times weight\ (in\ kg)}{serum\ creatinine\ (in\ \mu mol/L) \times 72 \times 0.0113}$$

Female:

$$CL_{CR}\ (mL/min) = \frac{[140 - age\ (in\ years)] \times weight\ (in\ kg)}{serum\ creatinine\ (in\ \mu mol/L) \times 72 \times 0.0113} \times 0.85$$

10.3.2. New York Heart Association (NYHA)

The NYHA classifications are summarized below.[20]

Table 10.2: New York Heart Association classifications

Class	Functional Capacity	Objective Assessment
I	Subjects with cardiac disease but without resulting limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.	**A.** No objective evidence of cardiovascular disease.
II	Subjects with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.	**B.** Objective evidence of minimal cardiovascular disease.
III	Subjects with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea, or anginal pain.	**C.** Objective evidence of moderately severe cardiovascular disease.
IV	Subjects with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.	**D.** Objective evidence of severe cardiovascular disease.

Source: American Heart Association. Classification of Functional Capacity and Objective Assessment, Ninth edition March 14, 1994.

http://my.americanheart.org/professional/StatementsGuidelines/ByPublicationDate/PreviousYears/Classification-of-Functional-Capacity-and-Objective-Assessment_UCM_423811_Article.jsp

10.3.3. CYP3A4 Inhibitors and Inducers

Table 10.3: Common CYP3A Inhibitors and Inducers CYP3A4 Inhibitors

Strong Inhibitors	Moderate inhibitors	Strong Inducers
• Boceprevir	• Aprepitant	• Apalutamide
• Clarithromycin	• Ciprofloxacin	• Carbamazepine
• Cobicistat	• Conivaptan	• Enzalutamide
• Danoprevir and ritonavir	• Crizotinib	• Mitotane
• Elvitegravir and ritonavir	• Cyclosporine	• Phenytoin
• Grapefruit juice, seville orange juice	• Diltiazem	• Rifampin
• Idelalisib	• Dronedarone	• St. John's wort
• 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 Jun 2020). Available from: https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers

10.3.4. Highly Effective Contraception

As multiple doses of pexidartinib may decrease the efficacy of hormonal contraceptives, female subjects of reproductive potential should use an effective, non-hormonal method of contraception. Methods considered to be highly effective contraception include:[21]

- Intrauterine device
- Bilateral tubal occlusion
- Vasectomy
- Complete sexual abstinence

10.4. Appendix 4: General Information - Adverse Events

10.4.1. Definition of Adverse Event

An AE is any untoward medical occurrence in a subject administered a pharmaceutical product and that does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal 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.[22]

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

Events Meeting the AE Definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically relevant in the medical and scientific judgment of the Investigator (ie, not related to progression of underlying disease).
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.

Events NOT Meeting the AE Definition

- Any clinically relevant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the subject's condition.

- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the subject's condition.
- Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE.
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.4.2. Serious Adverse Event

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

- Results in death
- Is life-threatening
  - The term 'life-threatening' in the definition of 'serious' refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe
- Requires inpatient hospitalization or prolongation of existing hospitalization
  - In general, hospitalization signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.
  - Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline or for administration of anticancer therapy after discontinuation of study drug is not considered an AE.
- Results in persistent or significant disability/incapacity
  - The term disability means a substantial disruption of a person's ability to conduct normal life functions.
  - This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea,

influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

- Is a congenital anomaly/birth defect
- Is an important medical event
- Medical or scientific judgment should be exercised in deciding whether SAE 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 medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.
  - Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

10.4.3. Grade Assessment

The severity of AEs will be graded using the latest NCI-CTCAE (version 5.0). For each episode, the highest severity grade attained should be reported.

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.

- Grade 1: Mild AE
- Grade 2: Moderate AE
- Grade 3: Severe AE
- Grade 4: Life-threatening consequences; urgent intervention indicated
- Grade 5: Death related to AE

Difference between Severity and Seriousness

The term "severe" is often used to describe the intensity (severity) of a specific event (as in mild, moderate, or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as severe headache). This is not the same as "serious," which is based on subject/event outcome or action criteria usually associated with events that pose a threat to a subject's life or functioning. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

10.4.4. Causality Assessment

The Investigator should assess causal relationship between an AE and the study drug based on 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).

10.4.5. 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 drug completed/permanently discontinued prior to reaction/event, or reaction/event occurred prior to start of treatment
- Unknown: Subject is lost to follow-up

10.4.6. Other Action Taken for Event

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

10.4.7. Adverse Event Outcome

- Recovered/Resolved
  - The subject fully recovered from the AE with no sequelae observed.

- Recovered/Resolved with Sequelae
  - The subject fully recovered from the AE but with sequelae.
- Recovering/Resolving
  - The AE is improving but not recovered
- Not Recovered/Not Resolved
  - The AE continues without improving.
- Fatal
  - Fatal should be used when death is a direct outcome of the AE
- Unknown

10.5. Appendix 5: Instructions Related to Severe Acute Respiratory Syndrome Coronavirus 2

Due to the potential impact of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), ie COVID-19, on subject safety, the Sponsor recommends the following dose modification and management plan for subjects with confirmed or suspected SARS-CoV-2 while being treated with pexidartinib. **Use CTCAE version 5.0 general grading criteria to evaluate SARS-CoV-2.** All dose modifications (discontinuation, interruptions or reductions) must be recorded on the AE and drug administration eCRFs.

Dose Modification for Suspected or Confirmed SARS-CoV-2

If SARS-CoV-2 infection is suspected, interrupt pexidartinib and rule out SARS-CoV-2 per local guidance.

- If SARS-CoV-2 is ruled out, follow dose modification and management guidance as outlined in Table 6.3.
- If SARS-CoV-2 is confirmed or is still suspected after evaluation, dosing of the investigational product should be withheld until consultation with the DS Medical Monitor is completed. In the event that a participant tests positive for SARS-CoV-2, or if testing is not available, Investigators should withhold dosing until such time as the symptoms resolve. If a positive SARS-CoV-2 test result is reported, consult with the DS Medical Monitor on whether resolution of symptoms alone without retesting is adequate to resume dosing of the investigational product. Investigators may consider dose modification of the study drug according to the subject's condition and after discussion with the study Medical Monitor or designee and manage SARS-CoV-2 per local guidance until recovery of SARS-CoV-2. SARS-CoV-2 recovery is defined as no signs/symptoms of SARS-CoV-2, at least 1 negative real-time reverse transcription polymerase chain reaction (RT-PCR) test result, and nearly or completely resolved chest CT findings.

PK Assessment(s) if Chloroquine or Hydroxychloroquine is Administered

Additional PK serum samples should be collected if chloroquine (CQ) or hydroxychloroquine (HCQ) is administered for SARS-CoV-2 infection at the time points specified in the Schedule of Assessments (Section 1.3).

The chloroquine or HCQ administration time and the exact time of blood sample collection for PK analysis must be recorded on the eCRF.

SARS-CoV-2 Assessment(s)

All confirmed or suspected SARS-CoV-2 infection events must be recorded in the eCRF. If a subject presents to the clinic with symptoms suggestive of SARS-CoV-2, but the real-time RT-PCR test is not available at the site, a nasopharyngeal swab/saliva sample kit will be provided for sample collection to be tested at a central laboratory. The results will be provided to the site from the central laboratory.

Serum samples will be used for SARS-CoV-2 testing from each subject who provides consent. Samples will be collected prior to the study drug dosing, shipped to a central laboratory, and stored there until the tests become available.

If subjects consent, the remaining serum samples will also be stored for future analysis.

Serum, nasopharyngeal swab/saliva, and PK sample collection, preparation, handling, storage, and shipping instructions are provided in the Study Laboratory Manual.

Statistical Analysis - Assessment of the Impact of SARS-CoV-2

If deemed appropriate, analyses will be performed to explore the impact of SARS-CoV-2 on the safety and efficacy results reported for the study.

As a result of the impact of SARS-CoV-2 on study conduct, adjustments to the statistical analysis and interpretation will be made, if required. These will be described in the SAP.

10.6. Appendix 6 Key Data Analysis Requirements

Table 10.4: Key Data Requirements

Endpoint/Analysis	Key Data Requirements
Primary endpoint in Part 1 - DLT	All eCRF collected data and key external source data (eg. AEs and other safety data)
Primary endpoint in Part 2 - ORR	All tumor assessment data as assessed by centrally reviewed MRI scan based on RECIST 1.1 are required.

AE = adverse event; DLT = dose-limiting toxicity; eCRF = electronic case report form; MRI = magnetic resonance imaging; ORR = objective response rate; RECIST 1.1 = Response Evaluation Criteria in Solid Tumors Version 1.1.

10.7. Appendix 7 Patient Reported Outcomes, Surgical Assessment Questionnaire, and Long-Term Follow-up Questionnaire

10.7.1. Surgical Assessment Questionnaire

Table 10.5: 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

10.7.2. Long-Term Follow-up Questionnaire

Table 10.6: 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; MRI = magnetic resonance imaging; NE = not evaluable; PD = progressive disease; PR = partial response; SD = stable disease; TGCT = tenosynovial giant cell tumor

10.8. Appendix 8 Supplement List

Supplements are printed separately from the protocol, and their versions are independent from the study protocol.

Supplements are listed as follow:

- Supplement 1: Serious Adverse Event Report Form
- Supplement 2: Exposure In Utero Reporting Form
- Supplement 3: Compensation and Insurance
- Supplement 4: Study Administrative Structure

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12. LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse event
AESI	Adverse events of special interest
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AMA	Anti-mitochondrial antibody
AR	Observed accumulation ratio
AST	Aspartate aminotransferase
AUCt (*e.g.* AUC6h)	Area under the plasma concentration-time curve up to time t
AUCinf	Area under the plasma concentration-time curve up to infinity
AUClast	Area under the plasma concentration-time curve up to the last quantifiable time
BID	Twice a day
BOR	Best overall response
BPI	Brief pain inventory
C1D1	Cycle 1 Day 1
CFR	Code of federal regulations
CI	Confidence interval
CL_{CR}	Creatinine clearance
CL/F	Apparent total body clearance
Cmax	Maximum plasma concentration
CQ	Chloroquine
CR	Complete response
CRO	Contract research organization
CSF-1	Colony stimulating factor 1
CSF1R	Colony-stimulating factor 1 receptor
CSR	Clinical Study Report
CTCAE	Common terminology criteria for adverse events
Ctrough	Trough plasma concentration
CYP	Cytochrome P450
DLT	Dose-limiting toxicity
DoR	Duration of response
DS	Daiichi Sankyo

Abbreviation	Definition
EC	Ethical committee
ECG	Electrocardiogram
ECHO	Echocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic data capture
EIU	Exposure in utero
ELISA	Enzyme-linked immunosorbent assay
EOS	End of Study
EQ-5D-5L	The five-level version of EuroQol five-dimensional questionnaire
FAS	Full analysis set
FDA	Food and Drug Administration
FISH	Fluorescence in situ hybridization
FLT3	FMS-like tyrosine kinase 3
FSH	Follicle-stimulating hormone
GCP	Good Clinical Practice
GCT-TS	Giant cell tumor of the tendon sheath
GGT	Gamma-glutamyl transpeptidase
H2	histamine 2
HCQ	Hydroxychloroquine
HEAC	Hepatic adjudication committee
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICMJE	International Council of Medical Journal Editors
IEC	Independent ethics committee
IgG	Immunoglobulin G
IgM	Immunoglobulin M
INR	International normalized ratio
IRB	Institutional review board
IRT	Interactive response technology
ITD	Internal tandem duplication
Kel	Elimination rate constant associated with the terminal phase
KIT	KIT proto-oncogene receptor tyrosine kinase

Abbreviation	Definition
LH	Luteinizing hormone
LTFU	Long-term follow-up
LVEF	Left ventricular ejection fraction
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic resonance imaging
MUGA	Multigated acquisition
NCI	National Cancer Institute
NE	Not evaluable
NGS	Next generation sequencing
NRS	Numeric Rating Scale
NYHA	New York Heart Association
ORR	Objective response rate
OTC	Over-the-counter
P-CAB	Potassium-competitive acid blocker
PD	Progressive disease
Pdy	Pharmacodynamic(s)
PGx	Pharmacogenomic(s)
PK	Pharmacokinetic(s)
PopPK	Population pharmacokinetic(s)
PPI	Proton pump inhibitor
PR	Partial response
PRO	Patient-reported outcomes
PROMIS	Patient-Reported Outcomes Measurement Information System
Pt	Patient
PVNS	Pigmented villonodular synovitis
QTc	Corrected QT interval
QTcF	QT interval corrected with Fridericia's formula
RECIST	Response Evaluation Criteria in Solid Tumors
ROM	Range of motion
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2, ie COVID-19
SAVER	Serious Adverse Event Report
SCR	Screening

Abbreviation	Definition
SD	Stable disease
SID	Subject identifier
SMC	Safety monitoring committee
SOP	Standard operating procedures
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 to reach maximum plasma concentration
TVS	Tumor Volume Score
Tx	Treatment
t1/2	Terminal half-life
UGT	Uridine 5'-diphospho-glucuronosyltransferase
ULN	Upper limit of normal
US	United States
Vz/F	Apparent volume of distribution based on the terminal phase
WORMS	Whole-organ MRI score

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