CLINICAL STUDY PROTOCOL

A PHASE 4, MULTICENTER STUDY TO EVALUATE DISCONTINUATION AND RE-TREATMENT IN SUBJECTS WITH TENOSYNOVIAL GIANT CELL TUMOR (TGCT) PREVIOUSLY TREATED WITH PEXIDARTINIB

PEXIDARTINIB TGCT CONTINUATION STUDY

PROTOCOL NUMBER: PL3397-A-U4003

IND NUMBER: 117,332

NCT NUMBER: NCT04526704

[EudraCT NUMBER: 2020-000192-20]

VERSION 2.0, 25 Feb 2022

DAIICHI SANKYO, INC.

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INVESTIGATOR AGREEMENT

A Phase 4, multicenter study to evaluate the discontinuation and re-treatment in subjects with tenosynovial giant cell tumor (TGCT) previously treated with pexidartinib

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
2.0	25 Feb 2022
1.0	21 Feb 2020

SUMMARY OF CHANGES

Please refer to the comparison document for protocol V2.0 (dated 25 Feb 2022) versus protocol V1.0 (dated 21 Feb 2020) for actual changes in text. The summary of changes below is a topline summary of major changes in the current PL3397-A-U4003 clinical study protocol (V2.0) by section.

Amendment Rationale:

This amendment is for clarification updates to the scheduled visits and required assessments for operational and clinical safety purposes. Additionally, language has been added for the collection of COVID-19-related data.

CONVENTIONS USED IN THIS SUMMARY OF CHANGES		
All locations (Section numbers and/or paragraph/bullet numbers) refer to the current protocol version, which incorporates the items specified in this Summary of Changes document.		
Minor edits, such as update to language that does not alter original meaning, update to version numbering, formatting, change in font color, corrections to typographical errors, use of abbreviations, moving verbiage within a section or table, change in style, or change in case, are not noted in the table below.		
Section # and Title	**Description of Change**	**Brief Rationale**
• Cover page • 1.1 Protocol Synopsis	Added NCT number	NCT number was received
• Investigator Agreement	Removed Sponsor signature section	Veeva Vault electronic signature page to replace sponsor wet-ink signature
• 1.1 Protocol Synopsis • 5.1 Inclusion Criteria	Updated contraception language for donating sperm/ova during study treatment	Updated language for additional clarity
• Table 1.1 Schedule of Events: Treatment Continuation Cohort • Table 1.2 Schedule of Events: Treatment-Free Period of Treatment-Free/Re-Treatment Cohort • Table 1.3 Schedule of Events: Re-Treatment Period of Treatment-Free/Re-Treatment Cohort	Updated all 3 Schedule of Events tables to: • Add clarifying language for ECG timing (moved from vitals assessments) and frequency (also in Section 8.4.5 Other Safety) • Separate out TSH from hormone testing (also in Section 8.4.3 Clinical Laboratory Evaluations and Table 10.1 Clinical Laboratory Tests) • Update visits when dosing diary is provided to patients • Add a row for collection of End of Study form • Defined a month as a 28-day interval for the M1/M2 visit for retreatment patients in the Treatment-Free/Re-Treatment	Updated to more accurately reflect the visit schedules and the required assessments

CONVENTIONS USED IN THIS SUMMARY OF CHANGES		
	Cohort and as a 30-day interval for all other cohorts/visits (Table 1.1 and 1.3 only) • Clarified that MRI scans are required every 6 months for subjects in the Treatment Continuation Cohort and every 3 months for those in the Treatment-free period and Re-Treatment periods of the Treatment-Free/Re-Treatment Cohort (also in Sections 1 Protocol Summary and 4.1.1 Design Overview) • Clarified that subjects from Treatment Free/Re-Treatment Cohort restarting treatment should note MRI as due to progression and use the BL2 assessment as reference (also in Section 4.1.1 Design Overview) • Clarified that urinalysis assessments will be performed at 6-month intervals (also in Section 1 Protocol Summary) • Separated EOT and EOS/AE Follow-up as 2 separate visits and reinforced that EOT must occur within 24 months after enrollment • Removed entry for on-site study drug administration (also in Section 6.2.2 Administration) (Table 1.2 only) • Updated visits to: o make M12 its own visit o combine M24 and EOT o make EOS/AE Follow-up its own visit • Removed comments language for AE and ConMed rows	
• 4.1.1 Design Overview • Table 10.1 Clinical Laboratory Tests	Added coagulation, ECG, and hormone testing to list of ongoing safety monitoring and made albumin globulin (A/G) ratio optional	Completeness of list
• 4.1.3 Dose Regimen • 6.1 Study Drug(s) Description	Reinforced message that dose escalations are not permitted	Reinforcing existing language
• Section 4.1.4 Duration	Clarified frequency of study assessments for the Re-Treatment period of the Treatment-Free/Re-Treatment Cohort	Updated language for additional clarity

CONVENTIONS USED IN THIS SUMMARY OF CHANGES		
• 6.6 Prior and Concomitant Medications • 8.4.1 Adverse Event • 8.4.4 Reporting of Exposure to COVID-19 (SARS-CoV-2 • 9.5.2 Safety Analyses	Updated instructions on recording COVID-19 vaccination data and reporting COVID-19-associated AEs	Updated for clarity of instructions
• 8.4.1.1 Serious Adverse Event Reporting	Added overdose	Added for completeness of list
• 9.5.2 Safety Analyses	Added text that descriptive statistics would be provided for ECG	Updated for completeness
• Table 10.1 Clinical Laboratory Tests	Updated Table 10.1 • Removed bicarbonate test • Updated creatinine clearance to be defined by Cockcroft-Gault equation • Required PTT only if aPTT isn't collected • Required FSH and TSH at Baseline-only	Removed bicarbonate as being unnecessary for this indication and updated other language for clarity of instructions
• 10.3.2 CYP3A4 Inhibitors and Inducers	Clarified that list of CYP3A4 inhibitors and inducers is not complete	Added language for accuracy and completeness

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1. PROTOCOL SUMMARY

1.1. Protocol Synopsis

Protocol Title
A Phase 4, Multicenter Study to Evaluate Discontinuation and Re-Treatment in Subjects with Tenosynovial Giant Cell Tumor (TGCT) Previously Treated with Pexidartinib
Protocol Short Title
Pexidartinib TGCT Continuation Study
Protocol Number
PL3397-A-U4003
Sponsor/Collaborators
Daiichi Sankyo Inc Daiichi Sankyo Europe GmbH, a Daiichi Sankyo Company
Registry Identification(s)
• NCT Number: NCT04526704 • EudraCT Number: 2020-000192-20
IND Number
117,332
Study Phase
Phase 4
Planned Geographical Coverage, Study Sites, and Location
US, EU (Netherlands, Spain, Hungary, and Italy), Australia, and Taiwan
Study Population
Subjects with TGCT (pigmented villonodular synovitis [PVNS] or giant cell tumor of the tendon sheath [GCT-TS]) who are currently being treated with pexidartinib in one of the following studies (hereafter referred to as prior study): PLX108-10 (ENLIVEN), PLX108-01, PL3397-A-A103, or PL3397-A-U126.

Study Objectives/Outcome Measures and Endpoints

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

I. Treatment-Free/Re-Treatment Cohort

Period	Objectives	Outcome Measure	Endpoints	Category
Primary Objective				
Overall	Proportion of subjects who remain treatment-free	**Title:** Proportion of treatment-free subjects at 12 months and 24 months **Description:** Proportion of subjects who remain treatment-free at Month 12 and Month 24 **Time frame:** 24 months after last subject enrolled in the Cohort	Proportion of subjects who remain treatment-free at Month 12 and Month 24	Efficacy
Secondary Objectives				
Treatment-Free period	Change from Baseline in Patient Reported Outcomes (PROs)	**Title:** Change from Baseline in PROs **Description:** Change from Baseline in PROs (PROMIS PF, EQ-5D-5L) **Time frame:** 24 months after last subject enrolled in the Cohort	Mean change from Baseline* for PROMIS PF and EQ-5D-5L quarterly for the treatment-free and Re-Treatment periods. ***Note:** Baseline is Screening values.	Efficacy
	Safety	**Title:** Number of subjects with AE during the Treatment-Free period* **Description:** Total number of subjects in the safety analysis set with any AE collected between Screening and start of re-treatment or final database lock (whichever occurs first) **Time frame:** 24 months after last subject enrolled in the Cohort ***Note:** Listed as a secondary objective but is a primary outcome measure.	Incidence of AEs and SAEs, ECGs, and laboratory assessments	Safety
Re-Treatment period	Tumor Assessment	**Title:** Tumor assessment **Description:** Investigator evaluation of tumor **Time frame:** 24 months after last subject enrolled in the Cohort	Qualitative assessment of the tumor	Efficacy
	Change from Baseline in Patient Reported Outcomes (PROs)	**Title:** Change from Baseline in PROs **Description:** Change from Baseline in PROs (PROMIS PF, EQ-5D-5L) **Time frame:** 24 months after last subject enrolled in the Cohort	Mean change from Baseline* for PROMIS PF and EQ-5D-5L quarterly for the retreatment periods. ***Note:** Baseline is reinitiated with subject entering Re-Treatment period.	Efficacy
	Safety	**Title:** Number of subjects with AE during the Re-Treatment period* **Description:** Total number of subjects in the safety analysis set with any AE collected between first re-treatment dose and final database lock **Time frame:** 24 months after last subject enrolled in the Cohort ***Note:** Listed as a secondary objective but is a primary outcome measure.	Incidence of TEAEs and SAEs, ECGs, and laboratory assessments	Safety

II. Treatment Continuation Cohort

Objectives	Outcome Measure	Endpoints	Category
Primary Objective			
None			
Secondary Objectives			
Tumor Assessment	**Title:** Tumor assessment **Description:** Investigator evaluation of tumor **Time frame:** 24 months after last subject enrolled in the Cohort	Qualitative assessment of the tumor	Efficacy
Change from Baseline in PROs	**Title:** Change from Baseline in PROs **Description:** Change from Baseline in PROs (PROMIS PF, EQ-5D-5L) **Time frame:** 24 months after last subject enrolled in the Cohort	Mean change from Baseline* for PROMIS PF and EQ-5D-5L at quarterly assessments. ***Note:** Baseline is Screening values.	Efficacy
Safety	**Title:** Number of subjects with TEAE during the study* **Description:** Total number of subjects in the safety analysis set with any AE collected between first dose and final database lock **Time frame:** 24 months after last subject enrolled in the Cohort ***Note:** Listed as a secondary objective but is a primary outcome measure.	Incidence of TEAEs and SAEs, ECGs, and laboratory assessments	Safety

AE = adverse event; ECG = electrocardiogram; EQ-5D-5L = EuroQol-Five Dimension Five Level Scale; PRO = Patient-Reported Outcome ; PROMIS PF = Patient-Reported Outcomes Measurement Information System – Physical Function; SAE = serious adverse event; TEAE = treatment emergent adverse event

Study Design

This is a Phase 4, multicenter study in subjects with TGCT (PVNS or GCT-TS) who were previously treated with pexidartinib in one of the following studies: PLX108-10 (ENLIVEN), PLX108-01, PL3397-A-A103, and PL3397-A U126. At the Screening visit/time of consent, at the Investigator and subject's discretion, the subjects are given the choice to either continue treatment with pexidartinib or discontinue treatment with the possibility to reinitiate pexidartinib treatment.

1. Subjects who choose to continue treatment with pexidartinib will be enrolled in the **Treatment Continuation Cohort**. The assessments from the subject's "End-of-Treatment visit" (i.e., the visit on which they received their last dose of study treatment) from their prior study (eg, tumor assessments, PRO measures, and safety parameters) will serve as the Baseline measurements for PL3397-A-U4003 study. These subjects will remain on their current dosage of pexidartinib and undergo clinical assessments at 3-month intervals for the duration of the study.
2. Subjects who choose to discontinue pexidartinib treatment will be enrolled into the Treatment-Free period of the **Treatment-Free/Re-Treatment Cohort**. The assessments from the subject's End-of-Treatment visit from their prior study (eg, tumor assessments, PRO measures, and safety parameters) will serve as the Baseline measurements for PL3397-A-U4003 study. Subjects will discontinue pexidartinib treatment and undergo clinical assessments at 3-month intervals during the Treatment-Free period. Re-treatment with pexidartinib will be based on the discretion of the subject and Investigator. Tumor assessment, subjective and/or functional measures, and safety will be considered in the decision-making process. The rationale for discontinuing and restarting pexidartinib re-treatment will be recorded accordingly.

   Subjects in the **Treatment-Free/Re-Treatment Cohort** who enter the Re-Treatment period will be administered pexidartinib at the dose at which they completed the prior study. Dosing is required 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. During the Re-Treatment period, Investigators will ensure weekly liver monitoring tests for the first 8 weeks (2 months), then every 2 weeks for 1 month, then once every 3 months or more frequently as directed by the Investigator.

The Investigator will evaluate the MRI scans every 6 months for subjects in the Treatment Continuation Cohort and every 3 months for subjects in the Treatment-Free/Re-Treatment Cohort to perform a qualitative tumor assessment (i.e., stable disease) for subjects in the Treatment Continuation Cohort. Additional imaging assessments may be performed with changes in tumor response(s) as deemed necessary by the Investigator.

Patient Reported Outcomes (PROs) measures will be performed at 3-month intervals for all subjects.

Ongoing safety assessment, laboratory assessments (serum chemistry and hematology), and physical examination will be performed at 3-month intervals and monitored for adverse events (AEs). Note that laboratory assessments for urinalysis will be performed at 6-month intervals.

See Figure 1.1 for the study flow diagram.

Study Duration

The study start is the date when the first subject has signed the informed consent. Subjects will be evaluated for eligibility at the last visit of their prior study.

1. Subjects in the **Treatment Continuation Cohort** will remain on their current dosage of pexidartinib and undergo study assessments at 3-month intervals for a maximum of 24 months.
2. Subjects from the **Treatment-Free/Re-Treatment Cohort** who enter the Treatment-Free period will undergo study assessments 1 month after enrollment, 3 months after enrollment, and then at 3-month intervals for 24 months or until re-treatment with pexidartinib.

   Subjects from the **Treatment-Free/Re-Treatment Cohort** who enter the Re-Treatment period will undergo efficacy and safety study assessments at 3-month intervals until the total time within this Cohort reaches 24 months; a new Baseline will be established upon entry into re-treatment. Liver safety assessments will follow a separate schedule.

All subjects will remain on study for a maximum of 24 months. The study will end with the completion of the last subject's 30-day safety follow-up or with their withdrawal from the study. A post-trial access plan, delineating options for access to pexidartinib, will be available for subjects after completing their study participation if the subject is benefiting from the study drug.

Key Eligibility Criteria

Subjects must meet the following key inclusion/exclusion criteria:

Inclusion Criteria:

1. Currently enrolled and have not discontinued pexidartinib treatment in one of the following studies: Study PLX108-10 (ENLIVEN), Study PLX108-01, Study PL3397-A-A103, or Study PL3397-A-U126.
2. Willing and able to complete the PROMIS Physical Function Scale and EQ-5D-5L throughout the study.
3. Willing and able to provide written informed consent prior to any study-related procedures and to comply with all study requirements.
4. Females of reproductive potential must have a negative urine pregnancy test at Screening/Baseline (to be confirmed by a serum pregnancy test taken on the last-treatment visit of their prior study) and 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).

Note: A female is considered of reproductive potential following menarche and until becoming postmenopausal (no menstrual period for a minimum of 12 months) unless permanently sterile (undergone a hysterectomy, bilateral salpingectomy or bilateral oophorectomy) with a confirmed by follicle stimulating hormone (FSH) test level >40 mIU/mL.

5. Male subjects must not freeze or donate sperm starting at Screening and throughout the study period, and for at least 5 half-lives or 1 month after the final study drug administration, whichever is longer.

   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 or 5 half-lives after the final study drug administration, whichever is longer.

Exclusion Criteria:

1. Subject has a clinically significant abnormality identified by the Investigator at Screening on physical examination, laboratory tests, or electrocardiogram (ECG) which, in the judgement of the Investigator, would preclude the subject's safe completion of the study.
2. Exposure to another investigational drug or current participation in other therapeutic investigational procedures, besides pexidartinib studies, within 1 month prior to start of study treatment. Any known contraindication to treatment with, including hypersensitivity to, the study drug(s) or excipients in pexidartinib.

Investigational Medicinal Product, Dose, and Mode of Administration

Pexidartinib hydrochloride (HCl) drug substance is an off-white to white solid. Pexidartinib capsules are provided as 200 mg (200 mg free-base equivalent) hypromellose capsules for oral administration containing the following excipients: poloxamer 407, mannitol, crospovidone, and magnesium stearate.

Pexidartinib capsules will be orally administered daily at the subject's current dose of pexidartinib in Study PLX108-10 (ENLIVEN), Study PLX108-01, Study PL3397-A-A103, or Study PL3397-A-U126. Pexidartinib should 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

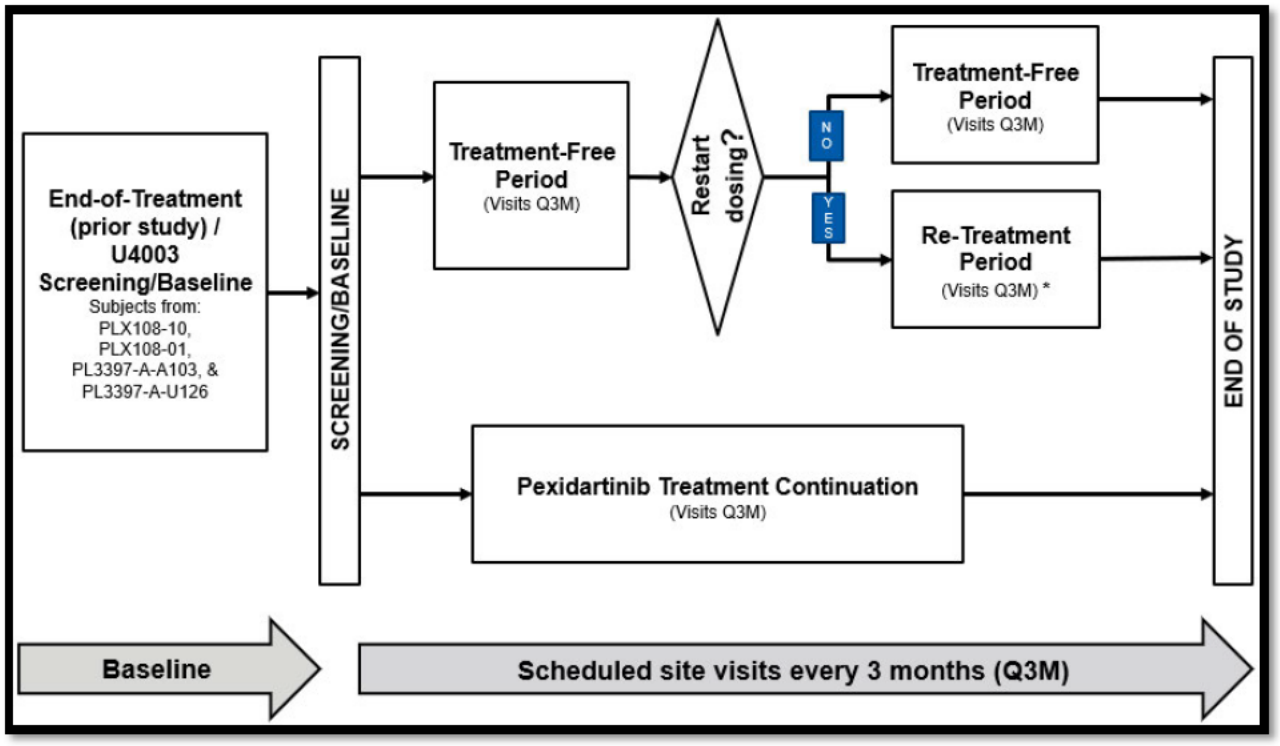
Pexidartinib (PLX3397)

Planned Sample Size

Subjects currently enrolled in Studies PLX108-10 (ENLIVEN), PLX108-01, PL3397-A-A103, and PL3397-A-U126 who are eligible for participation in this study.

1.2. Study Schema

Figure 1.1: Study Level Flow Diagram



* Subjects re-initiated on pexidartinib will undergo weekly liver monitoring tests for the first 8 weeks, then every 2 weeks for 1 month, then every 3 months or more frequently as directed by the Investigator.
Note: Screening and Baseline visits will occur on the same day.

1.3. Schedule of Events

Table 1.1: Schedule of Events: Treatment Continuation Cohort

	Visits	SCR	BL	M3	M6	M9	M12	M15	M18	M21	EOT[a]	EOS/ AE F/U[b]	Comment
	Window (Days)	**0***	**0***	**±7**	**±7**	**±7**	**±14**	**±14**	**±14**	**±14**	**±7**	**±7**	*** SCR and BL will both occur on EOT visit of preceding study.**
Assessments	**Procedure**												
Informed consent		X											Obtain prior to performing any study procedures
Eligibility assessment			X[c]										
Demographics/Medical history/Prior medications, non-drug therapies, and radiotherapy/Height	N/A												This information will be transferred from prior studies
Vitals	Vital signs and weight	X	X[c]	X	X	X	X	X	X	X	X		
PRO instruments	EQ-5D-5L		X[c]	X	X	X	X	X	X	X	X		Performed before any physical tests
	PROMIS PF		X[c]	X	X	X	X	X	X	X	X		Physical Function Scale performed before any physical tests
Safety	Physical exam	X	X[c]	X	X	X	X	X	X	X	X		Full PE on Screening and EOS, abbreviated PE at other visits. All PE exams will include functional assessment for the affected joint.
	ECG	X	X[c]								X		May be performed whenever deemed medically necessary and at any visit during which a subject exhibits a heart rate ≤50 bpm. Any abnormal finding should be confirmed with a repeated ECG. ECGs should be performed after vital signs assessments.

	Visits	SCR	BL	M3	M6	M9	M12	M15	M18	M21	EOT[a]	EOS/ AE F/U[b]	Comment
	Window (Days)	**0***	**0***	**±7**	**±7**	**±7**	**±14**	**±14**	**±14**	**±14**	**±7**	**±7**	*** SCR and BL will both occur on EOT visit of preceding study.**
Assessments	**Procedure**												
AE	TEAE/SAE		X[c]	X								X	See Section 8.4.1
Concomitant medications, non-drug therapies, and radiotherapy	Concomitant		X[c]	X									
Laboratory assessments	Hematology		X[c]	X	X	X	X	X	X	X	X		See Section 10.2 for details
	Chemistry		X[c]	X	X	X	X	X	X	X	X		See Section 10.2 for details
	Urinalysis		X[c]		X		X		X		X		See Section 10.2 for details
	Coagulation		X[c]	X	X	X	X	X	X	X	X		See Section 10.2 for details
	Serum pregnancy test	X	X[d]								X		For females of reproductive potential (as defined in Section 5.1)
	Liver function tests		X	X	X	X	X	X	X	X	X		AST, ALT, ALP, total bilirubin, GGT, direct bilirubin
	Hormone testing		X[c]										Females only, FSH to confirm postmenopausal status
	TSH	X	X										
Treatment response/Disease assessment	MRI of affected joint		X[c]		X		X		X		X[e]		Tumor assessment. Additional imaging assessments may be performed with changes in tumor response(s), as deemed necessary by the Investigator.
Dosing Diary	Provide Diary		X	X	X	X	X	X	X	X			Diary for pill count and AEs between scheduled clinic visits
	Review Diary			X	X	X	X	X	X	X	X		

	Visits	SCR	BL	M3	M6	M9	M12	M15	M18	M21	EOT[a]	EOS/ AE F/U[b]	Comment
	Window (Days)	**0***	**0***	**±7**	**±7**	**±7**	**±14**	**±14**	**±14**	**±14**	**±7**	**±7**	*** SCR and BL will both occur on EOT visit of preceding study.**
Assessments	**Procedure**												
Study Drug: Pexidartinib	Dispense 3-month supply		X	X	X	X	X	X	X	X			
	Collect returned/ Assess treatment compliance		X	X	X	X	X	X	X	X	X		
EOS Form												X	

AE = adverse event; BL = baseline; D = day; ECG = electrocardiogram; EOS = End of Study; EOT = End of Treatment; EQ-5D-5L = European Quality of Life Five Dimension Five Level Scale; FSH = follicle stimulating hormone; FU = Follow-up; M = month; MRI = magnetic resonance imaging; PRO = Patient-Reported Outcome; PROMIS PF = Patient-Reported Outcomes Measurement Information System – Physical Function; SAE = serious adverse events; SCR = screening; TEAE = treatment emergent adverse events; TVS = tumor volume score.

Note: For all visits, a month is considered a 30-day interval.

[a] The EOT visit should occur within 7 days after the last dose of pexidartinib or at the time the decision is made to discontinue pexidartinib (if this is more than 7 days after the last dose of pexidartinib), unless there is a medical condition that prevents subjects from completing the visit within this time. The EOT visit must occur within 24 months after enrollment.

[b] The End-of-Study will be reached with a follow-up phone call 1-month post-EOT visit to collect AE information.

[c] Assessment does not need to be repeated if the procedure was done at End-of-Treatment visit of preceding study.

[d] Urine pregnancy test at Screening only.

[e] Only subjects who end their study participation early with no radiologic disease progression will have an additional MRI at 3 months ± 14 days after their last dose of study treatment or before any new TGCT therapy, including surgery, whichever occurs first. EOS will occur after this additional MRI.

Table 1.2: Schedule of Events: Treatment-Free Period of Treatment-Free/Re-Treatment Cohort

	Visits	SCR	BL	M1	M3/ M15	M6/ M18	M9/ M21	M12[a]	M24	EOS/ AE F/U[b]	Comment
	Window (Days)	**0***	**0***	**+ 28**	**±14**	**±14**	**±14**	**±14**	**±14**	**±7**	**** SCR and BL will both occur on EOT visit of preceding study.**
Assessments	**Procedure**										
Informed consent		X									Obtain prior to performing any study procedures
Eligibility assessment			X								
Demographics/Medical history/Prior medications, non-drug therapies, and radiotherapy/Height	N/A										This information will be transferred from prior studies
Vitals	Vital signs and weight		X[c]	X	X	X	X	X	X		
PRO instruments	EQ-5D-5L		X[c]	X	X	X	X	X	X		Performed before any physical tests
	PROMIS PF		X[c]	X	X	X	X	X	X		Physical Function Scale performed before any physical tests
Safety	Physical exam		X[c]	X	X	X	X	X	X		Full PE at Screening and EOS, abbreviated PE at other visits. All PEs will include functional assessment for the affected joint.
	ECG		X[c]						X		May be performed whenever deemed medically necessary and at any visit during which a subject exhibits a heart rate ≤50 bpm. Any abnormal finding should be confirmed with a repeated ECG. ECGs should be performed after vital signs assessments.
AE	AE/SAE		X[c]	X						X	
Concomitant medications, non-drug therapies, and radiotherapy	Concomitant		X[c]	X							

	Visits	SCR	BL	M1	M3/ M15	M6/ M18	M9/ M21	M12[a]	M24	EOS/ AE F/U[b]	Comment
	Window (Days)	**0***	**0***	**+ 28**	**±14**	**±14**	**±14**	**±14**	**±14**	**±7**	**** SCR and BL will both occur on EOT visit of preceding study.**
Assessments	**Procedure**										
Laboratory assessments	Hematology		X[c]			X		X	X		See Section 10.2 for details
	Chemistry		X[c]			X		X	X		See Section 10.2 for details
	Urinalysis		X[c]			X		X	X		See Section 10.2 for details
	Coagulation		X[c]			X		X	X		See Section 10.2 for details
	Liver function tests		X			X		X	X		AST, ALT, ALP, total bilirubin, GGT, direct bilirubin
	Urine pregnancy test	X									
	Hormone testing	X[c]	X[c]								Females only, FSH to confirm postmenopausal status
	TSH	X									
Disease assessment	MRI of affected joint		X[c]	X	X	X	X	X	X		Tumor assessment
Dosing Diary	Provide Diary		X	X	X	X	X	X			Diary for AEs between scheduled clinic visits
	Review Diary			X	X	X	X	X	X		
EOS Form										X	

AE = adverse event; BL = baseline; D = day; ECG = electrocardiogram; EOS = End of Study; EOT = End of Treatment; EQ 5D 5L = European Quality of Life Five Dimension Five Level Scale; FSH = follicle stimulating hormone; FU = Follow-up; M = month; MRI = magnetic resonance imaging; PRO = Patient-Reported Outcome; PROMIS PF = Patient-Reported Outcomes Measurement Information System – Physical Function; SAE = serious adverse events; SCR = screening; TVS = tumor volume score.
Note: For all visits, a month is considered a 30-day interval.
Note: In case of early discontinuation from the study, subjects must complete all the assessments corresponding to the M24 visit.
[a] Subjects are allowed to continue past 12 months within the Treatment-Free period and will follow quarterly visits as per the 12-month visit until they enter the Re-Treatment period or the EOS, whereupon they will complete the EOS Visit and 30-day safety follow-up.
[b] The End-of-Study will be reached with a follow-up phone call 1-month post-last study visit to collect AE information.
[c] Assessment does not need to be repeated if the procedure was done at End-of-Treatment visit of preceding study.

Table 1.3: Schedule of Events: Re-Treatment Period[a] of Treatment-Free/Re-Treatment Cohort

	Visits	BL-2	M1, M2 (LFT)[a]	M3	M6	M9	Mx[b]	EOT[c]	EOS/ AE FU[d]	Comment
	Window (Days)	**0**	**±3**	**±3**	**±14**	**±14**	**±14**	**±7**		
Assessments	**Procedure**									
Vitals	Vital signs and weight	X	X	X	X	X	X	X		
PRO instruments	EQ-5D-5L	X		X	X	X	X	X		Performed before any physical tests
	PROMIS PF	X		X	X	X	X	X		Physical Function Scale performed before any physical tests
Safety	Physical exam	X	X	X	X	X	X	X		Full PE on EOS, abbreviated PE at first re-treatment and at other visits. All PEs will include functional assessment for the affected joint
	ECG	X						X		May be performed whenever deemed medically necessary and at any visit during which a subject exhibits a heart rate ≤50 bpm. Any abnormal finding should be confirmed with a repeated ECG. ECGs should be performed after vital signs assessments.
AE	TEAE/SAE	X							X	
Concomitant medications, non-drug therapies, and radiotherapy	Concomitant	X								
Laboratory assessments	Hematology	X	X	X	X	X	X	X		See Section 10.2 for details
	Chemistry	X	X	X	X	X	X	X		See Section 10.2 for details
	Urinalysis	X	X		X		X	X		See Section 10.2 for details. Only perform every 6 months (ie, M12, M18, and M24)
	Coagulation	X	X	X	X	X	X	X		See Section 10.2 for details
	Serum pregnancy test	X	X	X	X	X	X	X		For females of reproductive potential (as defined in Section 5.1)
	Liver function tests[a]	X	X[a]	X	X	X	X	X		

	Visits	BL-2	M1, M2 (LFT)[a]	M3	M6	M9	Mx[b]	EOT[c]	EOS/ AE FU[d]	Comment
	Window (Days)	**0**	**±3**	**±3**	**±14**	**±14**	**±14**	**±7**		
Assessments	**Procedure**									
	Hormone testing	X								Females only, FSH to confirm postmenopausal status
	TSH	X								
Treatment Response/ Disease Assessment	MRI of affected joint	X[e]		X	X	X	X	X[f]		Tumor assessment. Additional imaging assessments may be performed with changes in tumor response(s) as deemed necessary by the Investigator.
Dosing Diary	Provide Diary		X	X	X	X	X			Diary for pill count and AEs between scheduled clinic visits
	Review Diary			X	X	X	X	X		
Study Drug: Pexidartinib	Dispense 3-month supply	X		X	X	X	X			A drug supply for more than 3 months may be dispensed.
	Collect Returned/ Assess Treatment Compliance			X	X	X	X	X		
EOS Form									X	

AE = adverse event; BL = baseline; D = day; ECG = electrocardiogram; EOS = End of Study; EOT = End-of-Treatment; EQ-5D-5L = European Quality of Life Five Dimension Five Level Scale; FSH = follicle stimulating hormone; FU = Follow-up; M = month; MRI = magnetic resonance imaging; PRO = Patient-Reported Outcome; PROMIS PF = Patient-Reported Outcomes Measurement Information System – Physical Function; SAE = serious adverse events; SCR = screening; TEAE = treatment emergent adverse events; TVS = tumor volume score.

Note: For all visits, a month is considered a 30-day interval, except for the M1/M2 visit for re-treatment patients where there is a 28-day window.

[a] Pexidartinib will be administered at the dose at which subject completed the prior study. Doses will be taken 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. Weekly liver monitoring tests for the first 8 weeks, then every 2 weeks for 1 month, then every 3 months or more frequently as directed by the Investigator.

[b] Patient visits should be done every 3 Months until 21 Months after baseline. The combined overall study duration of all treatment, treatment-free, and re-treatment phases should not exceed 24 months.

[c] The EOT visit should occur within 7 days after the last dose of pexidartinib or at the time the decision is made to discontinue pexidartinib (if this is more than 7 days after the last dose of pexidartinib), unless there is a medical condition that prevents subjects from completing the visit within this time.

[d] The End-of-Study will be reached with a follow-up phone call 1-month post-EOT visit to collect AE information.

[e] BL2 MRI will need to be done within 14 days before treatment BL2 (window -14 days). Response should note "Progression" for those patients re-starting treatment. Assessments after re-treatment should use BL2 as the reference to determine Progression or Non-Progression.

[f] Only subjects who end their study participation early with no radiologic disease progression will have an additional MRI at 3 months ± 14 days after their last dose of study treatment or before any new TGCT therapy, including surgery, whichever occurs first. EOS will occur after this additional MRI.

2. INTRODUCTION

2.1. Background

2.1.1. Tenosynovial Giant Cell Tumor (TGCT)

Tenosynovial giant cell tumor (TGCT) is a rare, nonmalignant neoplasm of the synovium, bursae, or tendon sheaths that is driven by overexpression of colony-stimulating factor-1 (CSF-1) often afflicting adults under 40 years of age. Annual TGCT incidence is estimated to be 43 cases per one million individuals, of which approximately 10% are of the diffuse subtype. Surgical resection, when feasible, is the standard treatment for TGCT; however, recurrence of the diffuse subtype is particularly common. Repeated surgeries often result in increasing morbidity and functional limitations of the affected joints. The diffuse disease often has more extensive involvement and a poorer likelihood of a successful cure with surgery, and therefore often may not be amenable to surgical resection due to the risk of morbidity or high risk of recurrence in diffuse disease. Systemic therapies targeting CSF-1 activity are being evaluated for the treatment of TGCT.

2.1.2. Pexidartinib (PLX3397)

Pexidartinib is an oral small-molecule tyrosine kinase inhibitor that targets 3 kinases: CSF-1 receptor ([CSF-1R] or feline McDonough sarcoma [FMS] kinase); proto-oncogene receptor tyrosine kinase (c-Kit), and FMS-like tyrosine kinase 3. TURALIO™ (Pexidartinib) was approved, 02 Aug 2019, by the United States (US) Food and Drug Administration (FDA) for the treatment of symptomatic TGCT associated with severe morbidity or functional limitations and not amenable to improvement with surgery. Pexidartinib is the first systemic therapy to show a robust tumor response in TGCT with improved patient symptoms and functional outcomes; cholestatic hepatotoxicity has been identified as a risk. It was approved with a boxed warning for hepatotoxicity and is available only through a restricted program called the TURALIO Risk Evaluation and Mitigation Strategy (REMS) program.

The approval was based on the durable overall response rate (ORR) observed in the Phase 3 study PLX108-10 (ENLIVEN) which provided compelling evidence of its effectiveness for the treatment of subjects with TGCT. In the ENLIVEN study, an international, multicenter, randomized (1:1), double-blind, placebo-controlled study, 120 subjects with TGCT not amenable to surgical resection and treated with pexidartinib had a robust tumor response rate versus placebo at Week 25 by Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1 (39% vs 0%; $P<0.0001$) and by tumor volume score (TVS) (56% vs 0%; $P<0.0001$). Further evidence of tumor response and clinical improvements are noted in the TGCT extension cohort of Study PLX108-01, as well as the longer-term data from the ENLIVEN study.

The safety data showed serious adverse events (SAEs) occurred in 13% (8/61) of patients in the pexidartinib group and 2% (1/59) of patients in the placebo group. The most frequent pexidartinib-associated treatment-emergent adverse events (TEAEs) were hair color changes, fatigue, aspartate aminotransferase (AST) increase, nausea, alanine aminotransferase (ALT) increase, and dysgeusia. Pexidartinib was associated with 2 types of hepatic adverse reactions. The first was a dose-dependent, generally low-grade aminotransferase elevation related to the

CSF-1R inhibition mechanism of action. These elevations are primarily observed during the first 8 weeks of treatment. The second hepatic adverse reaction, mixed or cholestatic hepatotoxicity, which while rarely serious can be life-threatening, also generally appeared in the first 8 weeks of treatment, however, is uncommon and idiosyncratic in nature.

As noted, long-term follow-up showed further increases in tumor response with continued pexidartinib treatment. For long-term pooled efficacy and safety, 130 patients in ENLIVEN and PLX108-01 received pexidartinib; 47% (61) patients remained on treatment at data cut-off. Median follow-up from first dose to data cutoff was 23 months (range, 16, 67); median treatment duration was 17 months (range, 1, 60+). Four percent (5) patients discontinued pexidartinib due to progressive disease (PD). Pooled RECIST v1.1-based best overall response (BOR) was 54%, with increased BOR from longer treatment. The safety profile was consistent with earlier reports, with no new safety signals.

Currently, besides the ENLIVEN and PLX108-01 studies, there are 2 additional Phase 1/2 studies (Study PL3397-A-A103 and Study PL3397-A-U126) that are ongoing. The objectives of these 4 pexidartinib studies in TGCT have been met and the investigational sites are to be closed. Eligible subjects from these studies will be included in the subject population for this study.

Refer to the *Pexidartinib Investigator's Brochure (IB)* for additional details and information.

2.2. Study Rationale

Over time, with daily treatment, many patients on long-term use of pexidartinib in these studies achieved significant tumor responses. In the ENLIVEN study, with the 90-day post-treatment observation period, no cases of rapid tumor regrowth were observed, suggesting that quarterly follow-ups are of adequate frequency to identify any patients, who need to re-initiate their treatment. However, beyond the 3-month post-treatment follow-up in ENLIVEN, there are no data to fully understand the impact of discontinuing pexidartinib treatment in patients with stable and/or residual disease. And, with slow-growing disease like TGCT, 3 months is not sufficient to determine the time when the treatment needs to be restarted. Feasibility of intermittent on-off dosing remains an open medical question.

Patients with TGCT diagnosed early in their lives face potentially several decades of daily treatment. In the real-world setting, subjects and Investigators are faced with decisions surrounding patients' activities of daily living and treatment with pexidartinib for TGCT. Further data are necessary to fully understand the safe and effective discontinuation and re-treatment with pexidartinib therapy in this patient population.

The purpose of this Phase 4 multicenter study in subjects with TGCT previously treated with pexidartinib are two-fold. At the Screening visit/time of consent, the Investigators and subjects are provided the choice to either continue treatment with pexidartinib or discontinue treatment with the possibility of re-initiating pexidartinib treatment at a later time. Findings from this study will provide important prospective discontinuation and re-treatment data with pexidartinib in previously treated subjects with residual disease.

Ultimately, this study will contribute meaningful information to the body of research on pexidartinib treatment for patients with TGCT and the safe and effective discontinuation and re-treatment with pexidartinib therapy.

2.3. Benefit and Risk Assessment

As noted, in the Pexidartinib Clinical Development Program, pexidartinib has demonstrated statistically significant and clinically meaningful efficacy. The efficacy data from the ENLIVEN study provide evidence of its effectiveness for the treatment of subjects with TGCT. Further evidence of tumor response and clinical improvements are noted in the TGCT extension cohort of the PLX108-01, as well as the longer-term data from the ENLIVEN study.[6] The benefits for subjects treated with pexidartinib in these studies is expected to continue to be observed in this study.

Pexidartinib can cause hepatic adverse reactions, including aminotransferase abnormalities or mixed or cholestatic hepatotoxicity that may be fatal. Hepatotoxicity is an important adverse drug reaction (ADR). 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, in 1 case, transplantation. The mechanism of cholestatic hepatotoxicity is unknown, and its occurrence cannot be predicted.

Also, guidance on protocol-defined dose reductions, discontinuation of pexidartinib, increased frequency of laboratory monitoring, and reporting of findings have been established. After re-initiating treatment with pexidartinib the liver function tests AST, ALT, total bilirubin, direct bilirubin, alkaline phosphatase (ALP), and gamma-glutamyl transferase (GGT) will be monitored weekly for the first 8 weeks, every 2 weeks for 1 month, and every 3 months thereafter. The dose of pexidartinib will be reduced, withheld or permanently discontinued based on the severity of hepatoxicity. Re-challenge with pexidartinib is not to be attempted without prior discussion with the Sponsor's Medical Monitor.

Re-challenges with a reduced dose of pexidartinib may result in a recurrence of increased serum transaminases, bilirubin, or ALP. The mixed or cholestatic hepatotoxicity is idiosyncratic and may therefore recur with re-challenge. Therefore, liver function tests are to be monitored weekly for the first 2 months after re-challenge, then every 2 weeks for 1 month, and then once every 3 months or more frequently as directed by the Investigator. Both the Investigator and subjects will be educated by the Sponsor on the eligibility criteria, benefits/risks of pexidartinib, necessary liver monitoring testing and guidance on dose reduction, and discontinuation.

In addition, administration with food increases pexidartinib exposure by 100% and may increase the risk of hepatotoxicity. Therefore, Investigators and subjects are instructed that pexidartinib administration is to be on an empty stomach, at least 1 hour before or 2 hours after a meal or snack. Investigators and subjects will also be instructed to avoid concomitant use of pexidartinib with strong cytochrome P450 (CYP)3A inhibitors or uridine 5'-diphospho-glucuronosyltransferase (UGT) inhibitors during the study.

Refer to the *Pexidartinib IB* for additional details and information.

3. OBJECTIVES, OUTCOME MEASURES, AND ENDPOINTS

The objectives, definitions of associated endpoints, as well as applicable outcome measures are described in Table 3.1 and Table 3.2. Further requirements for the endpoint analyses and censoring rules, where applicable, can be found in Section 9.5.1, Section 9.5.2, and Section 9.5.3.

Table 3.1: Description of Objectives, Outcome Measures, and Endpoints (Treatment-Free/Re-Treatment Cohort)

Period	Objectives	Outcome Measure	Endpoints	Category
Primary Objective				
Overall	Proportion of subjects who remain treatment-free	**Title:** Proportion of treatment-free subjects at 12 months and 24 months **Description:** Proportion of subjects who remain treatment-free at Month 12 and Month 24 **Time frame:** 24 months after last subject enrolled in the Cohort	Proportion of subjects who remain treatment-free at Month 12 and Month 24	Efficacy
Secondary Objectives				
Treatment-Free period	Change from Baseline in Patient Reported Outcomes (PROs)	**Title:** Change from Baseline in PROs **Description:** Change from Baseline in PROs (PROMIS PF, EQ-5D-5L) **Time frame:** 24 months after last subject enrolled in the Cohort	Mean change from Baseline* for PROMIS PF and EQ-5D-5L quarterly for the treatment-free and Re-Treatment periods. ***Note**: Baseline is Screening values.	Efficacy
	Safety	**Title:** Number of subjects with AE during the Treatment-Free period* **Description:** Total number of subjects in the safety analysis set with any AE collected between Screening and start of re-treatment or final database lock (whichever occurs first) **Time frame:** 24 months after last subject enrolled in the Cohort ***Note**: Listed as a secondary objective but is a primary outcome measure.	Incidence of AEs and SAEs, ECGs, and laboratory assessments	Safety
Re-Treatment period	Tumor Assessment	**Title:** Tumor assessment **Description:** Investigator evaluation of tumor **Time frame:** 24 months after last subject enrolled in the Cohort	Qualitative assessment of the tumor	Efficacy
	Change from Baseline in Patient Reported Outcomes (PROs)	**Title:** Change from Baseline in PROs **Description:** Change from Baseline in PROs (PROMIS PF, EQ-5D-5L) **Time frame:** 24 months after last subject enrolled in the Cohort	Mean change from Baseline* for PROMIS PF and EQ-5D-5L quarterly for the Re-Treatment periods. ***Note**: Baseline is reinitiated with subject entering Re-Treatment period.	Efficacy
	Safety	**Title:** Number of subjects with AE during the Re-Treatment period*	Incidence of TEAEs and SAEs, ECGs, and laboratory assessments	Safety

Period	Objectives	Outcome Measure	Endpoints	Category
		Description: Total number of subjects in the safety analysis set with any AE collected between first re-treatment dose and final database lock **Time frame:** 24 months after last subject enrolled in the Cohort ***Note:** Listed as a secondary objective but is a primary outcome measure.		

AE = adverse event; EQ-5D-5L = EuroQol-Five Dimension Five Level Scale; PRO = Patient-Reported Outcomes ; PROMIS PF = Patient-Reported Outcomes Measurement Information System – Physical Function; SAE = serious adverse event; TEAE = treatment-emergent adverse event

Table 3.2: Description of Objectives, Outcome Measures, and Endpoints (Treatment Continuation Cohort)

Objectives	Outcome Measure	Endpoints	Category
Primary Objective			
None			
Secondary Objectives			
Tumor Assessment	**Title:** Tumor assessment **Description:** Investigator evaluation of tumor **Time frame:** 24 months after last subject enrolled in the Cohort	Qualitative assessment of the tumor	Efficacy
Change from Baseline in PROs	**Title:** Change from Baseline in PROs **Description:** Change from Baseline in PROs (PROMIS PF, EQ-5D-5L) **Time frame:** 24 months after last subject enrolled in the Cohort	Mean change from Baseline* for PROMIS PF and EQ-5D-5L at quarterly assessments. ***Note:** Baseline is Screening values.	Efficacy
Safety	**Title:** Number of subjects with TEAE during the study* **Description:** Total number of subjects in the safety analysis set with any AE collected between first dose and final database lock **Time frame:** 24 months after last subject enrolled in the Cohort ***Note:** Listed as a secondary objective but is a primary outcome measure.	Incidence of TEAEs and SAEs, ECGs, and laboratory assessments	Safety

AE = adverse event; ECG = electrocardiogram; EQ-5D-5L = EuroQol-Five Dimension Five Level Scale; PRO = Patient-Reported Outcomes ; PROMIS PF = Patient-Reported Outcomes Measurement Information System – Physical Function; SAE = serious adverse event; TEAE = treatment-emergent adverse event

3.1. Rationale for Selection of Primary and Key Secondary Endpoints

The primary and secondary endpoints were selected based on the clinical relevance and potential import for guiding the treatment of pexidartinib in patients with TGCT. Information on objective (tumor response), subjective (PROMIS-Physical Function Questionnaire, European Quality of Life Five Dimension Five Level Scale [EQ-5D-5L]), and safety measures for subjects with TGCT are all relevant for prescribers, patients, and regulators.

4. STUDY DESIGN

4.1. Overall Design

This is a Phase 4, multicenter study in subjects with TGCT (pigmented villonodular synovitis [PVNS] or giant cell tumor of the tendon sheath [GCT-TS]) who were previously treated with pexidartinib in one of the following studies (hereafter referred to as prior study): (PLX108-10 (ENLIVEN), PLX108-01, PL3397-A-A103, and PL3397-A U126). Based on these prior studies, subjects will be enrolled from investigational sites in the US, European Union (EU) (Netherlands, Spain, Hungary, and Italy), Australia, and Taiwan. The subject population is described in Section 5.

The study start date is the date when the first subject has signed an informed consent and the study end date will be the completion of the last patient's Follow-up Visit. A subject is eligible to be enrolled into the study when the Investigator or designee has determined the subject is currently receiving pexidartinib treatment as part of one of the prior studies and meets the inclusion/exclusion criteria for this study (Section 5).

4.1.1. Design Overview

Subjects in the 4 ongoing TGCT studies will be screened at the "End-of-Treatment (EOT) visit" (i.e., the visit at which they receive their final dose of pexidartinib) of their previous study, at which time they can elect to enroll in the PL3397-A-U4003 study in 1 of 2 cohorts – the **Treatment Continuation Cohort** (where their existing pexidartinib treatment will continue uninterrupted) or **Treatment-Free/ Re-Treatment Cohort** (where they will discontinue pexidartinib treatment with the possibility to re-initiate treatment over the course of the study). Subjects who elect to not enroll in the PL3397-A-U4003 study will remain in their current study and complete their respective End-of-Study activities.

Subjects who elect to enroll in PL3397-A-U4003 will sign an institutional review board (IRB)/independent ethics committee (IEC)-approved informed consent form (ICF). By signing the ICF, subjects will permit acquisition and data transfer of any data collected in their precursor study, including, but not limited to, medical and surgical history, and prior medications. The assessments performed during the preceding study's End-of-Treatment visit will serve as the Baseline measurements for the PL3397-A-U4003 study.

Eligible subject who choose to continue pexidartinib treatment in the **Treatment Continuation Cohort** will remain on their current dosage regimen of pexidartinib and undergo clinical assessments at 3-month intervals for the duration of the study.

Subjects who choose to discontinue pexidartinib will be enrolled in the Treatment-Free period of the **Treatment-Free/Re-Treatment Cohort**. These subjects will stop pexidartinib dosing at entry into PL3397-A-U4003 (i.e., after their final dose at the preceding study's EOT visit). Subjects will undergo clinical assessments 1 month after enrollment, 3 months after enrollment, and then at 3-month intervals. Subjects will remain treatment-free until retreated with pexidartinib, based on the Investigator and/or subject's discretion. Considerations are given to tumor response, subjective and/or functional measures, and safety parameters in the decision-making process. The rationale for discontinuation and re-treatment with pexidartinib will be recorded accordingly.

For subjects who restart pexidartinib treatment in the Re-Treatment period of the **Treatment-Free/Re-Treatment Cohort**, pexidartinib will be administered at the dosage level at which the subject completed the prior study. Doses 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 full set of study assessments will be performed (Baseline-2). During re-treatment, Investigators will ensure weekly liver monitoring tests for the first 8 weeks, then every 2 weeks for the next month, then every 3 months or more frequently as directed by the Investigator (see Table 6.3).

The Investigator will evaluate the quarterly magnetic resonance imaging (MRI) scans to perform a qualitative tumor assessment (i.e., stable disease) for subjects in the **Treatment-Free/Re-Treatment Cohort**. Additional assessments may be conducted based on worsening of tumor response as deemed necessary by the Investigator. For those subjects who restart pexidartinib treatment in the Re-Treatment period of the **Treatment-Free/Re-Treatment Cohort**, the response should note "Progression" and the assessments after re-treatment should use Baseline 2 as the reference to determine Progression or Non-Progression.

The PROs (PROMIS PF and EQ-5D-5L) will be performed every 3 months for all subjects.

Ongoing safety will include serum chemistry, hematology, urinalysis, coagulation, ECG, hormone testing, and physical examination, and subjects will be monitored for adverse events (AEs)/TEAEs.

Subjects on treatment who end their study participation early with no radiologic disease progression will undergo a final MRI 3 months ± 14 days after their last dose of study treatment or before any new TGCT therapy, including surgery.

Subjects who discontinue early from the study will complete the End-of-Study (EOS)/EOT visit and will be withdrawn from the study.

The subject population is described in Section 5. A flow diagram of the study is presented in Figure 1.1.

4.1.2. End of Study

The primary completion date is the date when the last of those subject(s) entering the Treatment-Free period of the **Treatment-Free/Re-Treatment Cohort** either progresses to and completes the Re-Treatment period and/or remains treatment-free for the duration of the study. This date is used as the cut-off date for the analysis of the primary efficacy endpoint(s) of the study.

The overall end of the study will occur when the last subject has their last visit/contact.

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

4.1.3. Dose Regimen

Pexidartinib will be provided as an oral, daily administration at the dosage level at the end of their prior study. Doses will be taken 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.

Note: Dose escalation of pexidartinib treatment is not permitted during the course of this study.

4.1.4. Duration

The study start date is the date when the first subject signs the ICF and the study continues until the last subject has had their last visit.

Duration of Treatment and Subject Participation

Subjects will be evaluated for eligibility at the last visit of their prior study.

Subject in the **Treatment Continuation Cohort** will undergo study assessments at 3-month intervals for a maximum of 24 months.

Subjects in the **Treatment-Free period of the Treatment-Free/Re-Treatment Cohort** will undergo study assessments at 1 month after enrollment, 3 months after enrollment, and then at 3-month intervals until either re-treatment with pexidartinib or for a maximum of 24 months.

Subjects in the **Re-Treatment period of the Treatment-Free/Re-Treatment Cohort** will undergo study assessments at M1, M2 and then at 3-month intervals. The maximum duration for any subject within the combined periods of the **Treatment-Free/Re-Treatment Cohort** is 24 months. Liver safety assessments will follow a separate schedule (See Table 1.3).

The study will end with the last subject's last visit. A post-trial access plan, delineating options for access to pexidartinib, will be available for subjects after completing their study participation if the subject is benefiting from the study drug.

Overall Study Duration

Anticipated total duration of the study is expected to be approximately 24 months. 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

A post-trial access plan, delineating options for access to pexidartinib, will be available for subjects after completing their study participation if the subject is benefiting from the study drug.

4.2. Rationale for Study Design

This Phase 4 study design assumes that in subjects with TGCT, having stable disease and who are being treated with pexidartinib, it is possible to suspend treatment until there are signs of disease progression. It is assumed that re-initiation of treatment with pexidartinib will again lead to stabilization of the subject's disease and potentially to a diminution of the disease.

4.3. Justification for Dose

The dose used during the subject's prior study was found to be safe and effective for the subject.

5. STUDY POPULATION

5.1. Inclusion Criteria

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

1. Currently enrolled and have not been discontinued from pexidartinib treatment in one of the following studies: Study PLX108-10 (ENLIVEN), Study PLX108-01, Study PL3397-A-A103, or Study PL3397-A-U126.
2. Willing and able to complete the PROMIS (Physical Function Scale) and EQ-5D-5L (European Quality of Life) throughout the study.
3. Willing and able to provide written informed consent form (ICF) prior to any study-related procedures and to comply with all study requirements.
4. Females of reproductive potential must have a negative urine pregnancy test at Screening/Baseline (to be confirmed by a serum pregnancy test taken on the End-of-Treatment visit of their prior study) and 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).

   Note: A female is considered of reproductive potential following menarche and until becoming postmenopausal (no menstrual period for a minimum of 12 months) unless permanently sterile (undergone a hysterectomy, bilateral salpingectomy or bilateral oophorectomy) with a confirmed by follicle stimulating hormone (FSH) test level >40 mIU/mL.
5. Male subjects must not freeze or donate sperm starting at Screening and throughout the study period, and for at least 5 half-lives or 1 month after the final study drug administration, whichever is longer.

   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 or 5 half-lives after the final study drug administration, whichever is longer.

5.2. Exclusion Criteria

Subjects who meet any of the following criteria are NOT eligible for enrollment into the study

1. Subject has a clinically significant abnormality identified by the Investigator at Screening on physical examination, laboratory tests, or electrocardiogram which, in the judgement of the Investigator, would preclude the subject's safe completion of the study.
2. Exposure to another investigational drug or current participation in other therapeutic investigational procedures, besides pexidartinib studies, within 1 month prior to start of study treatment. Any known contraindication to treatment with, including hypersensitivity to, the study drug(s) or excipients in pexidartinib.

5.3. Screening Failures, Rescreening, and Subject Replacement

If a subject does not meet eligibility criteria at Screening, they may be rescreened based on the Investigator's discretion. Details will be included in the *PL3397-A-U4003 Study Manual*.

6. STUDY TREATMENT(S)

See Figure 1.1 for treatment sequence.

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	Pexidartinib
Dosage Formulation	200 mg capsules
Dosage Level(s)	The dose level at end of prior study will serve as the starting dose level. Note: Dose escalation of pexidartinib treatment is not permitted during the course of this study.
Route of Administration	Oral
Dosing	Pexidartinib should be administered twice daily approximately 12 h apart on an empty stomach (at least 1 hour before or 2 hours after a meal or snack).
Duration	Daily until subject's end of study
Packaging	PLX3397-HCl 200 mg capsules are manufactured, packaged, and labeled according to Good Manufacturing Practices and Good Clinical Practices (GCP). Packaging will clearly display the name of product, storage condition, and other required information as applicable in accordance with local regulations.
Labeling	Packaging will be labeled as required per local regulatory requirement.

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

6.2.1. Preparation, Handling, and Disposal

All pexidartinib is supplied as 200-mg capsules that need no further preparation at the study sites.

Procedures for proper handling and disposal should be followed in compliance with the Standard Operating Procedures (SOPs) of the Investigational site.

6.2.2. Administration

Pexidartinib is provided as 200-mg capsules for oral, daily administration. Subjects are to be administered the dosage level at which they completed their prior study. Doses 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. Administration with food (particularly with high proportion of fat) may result in increased exposure to pexidartinib and should be avoided. Dose reductions and interruptions are permitted according to pre-specified guidelines.

On the day of the scheduled visit, subjects will be instructed to take their morning and evening dose at the usual time of study treatment. Subjects should be told to bring their bottle containing all unused study treatment to the clinic for accountability.

Between clinic visits, subjects will administer their study treatment at home and record the dosing information in the study dosing Diary. Missed doses (those generally outside of a ± 2-hour dosing window) should be skipped and **NOT** administered as a double dose at the next dosing time point. Subjects who vomit their dose should be instructed **NOT** to make up that dose. Study sites will call subjects on a weekly basis as reminders to bring IP bottles to site visits and to complete their diaries. During these calls, study sites may also collect other information, including AEs and concomitant medications.

Further details on study treatment administration are contained in the *PLX3397-A-U4003 Pharmacy Manual*.

6.2.3. Storage

Pexidartinib should be stored at the sites in a secure, controlled facility and only provided to subjects who signed an ICF and are participating in the study. Pexidartinib 200 mg capsules should be stored at controlled room temperature (should not be stored above 25°C/77°F). Excursions are permitted to 15°C to 30°C (59ºF to 86ºF). If storage conditions are not maintained per specified requirements, then the Sponsor or contract research organization (CRO) should be contacted. Subjects will be instructed to store pexidartinib at room temperature out of the reach of children or other cohabitants.

6.2.4. 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.

Documentation of receipt of shipment should be returned as instructed on the form. The original will be retained at the study site.

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

The Investigator is responsible for study drug accountability, reconciliation, and record maintenance (i.e., documentation of receipt of shipment, dispensation/return record, and certificate of destruction/return receipt).

Additional information can be found in the *PL3397-A-U4003 Study Manual*.

6.3. Measure to Minimize Bias: Randomization and Blinding

Not applicable.

6.4. Treatment Compliance

Dosing compliance for pexidartinib will be assessed by means of capsule counts remaining or bottles returned. All pexidartinib packaging will be returned at each subject visit; an accounting of capsules will be made and recorded in the electronic case report form (eCRF). If zero capsules were returned, subjects are asked whether any were disposed/thrown away, rather than

taken orally, and this information will be recorded in the eCRF. Subjects will record time and day of administration in the subject's Diary.

6.5. Guidelines for Dose Modification

Reduction or interruption of the dose for toxicity may take place at any time according to the guidelines in Table 6.3. Dose reduction/interruption guidelines for hematologic and non-hematologic treatment-related TEAEs are based on severity. Dose interruptions can be implemented at the discretion of the treating physician to manage intolerable or clinically significant toxicity. If a dose interruption is required, study assessments should be performed as scheduled, irrespective of the study treatment delay. Interruptions due to toxicity lasting >14 days require treatment discontinuation unless the Medical Monitor approves continuation.

The recommended dose reductions for AEs are provided in Table 6.2.

Table 6.2: Recommended Dose Reductions for Pexidartinib for Adverse Reactions

Dose Reduction	New 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

Subjects unable to tolerate 200 mg orally twice daily will be discontinued. Once dose reduction takes place for toxicity, a dose re-escalation is not allowed.

The recommended dosage of pexidartinib for patients with mild to severe renal impairment (creatinine clearance [CrCL] 15 to 89 mL/min estimated by Cockcroft-Gault using actual body weight, Section 10.3.1) is 200 mg in the morning and 400 mg in the evening.

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 physician. All adjustments should be communicated to the Sponsor's Medical Monitor or designee. Re-challenge with a reduced dose of pexidartinib may result in a recurrence of increased serum transaminases, bilirubin, or ALP. Investigators will ensure weekly liver monitoring tests for the first 8 weeks after re-challenge, then every 2 weeks for the next month, then every 3 months or more frequently as directed by the Investigator.

Additional information can be found in the *PL3397-A-U4003 Study Manual* and the *Pexidartinib IB*.

Table 6.3: Recommended Dosage Modifications for Pexidartinib for Adverse Reactions

Event	Severity	Pexidartinib Dosage Modifications
Hepatoxicity		
Increased ALT and/or AST	>3 to 5 × ULN	• Withhold and monitor liver tests weekly. • If AST and ALT ≤3 × ULN within 4 weeks, resume at reduced dose. • If AST or ALT not ≤3 × ULN in 4 weeks, permanently discontinue pexidartinib.

Event	Severity	Pexidartinib Dosage Modifications
	>5 to 10 × ULN	• Withhold and monitor liver tests twice weekly. • If AST and ALT ≤3 × ULN within 4 weeks, resume at reduced dose. • If AST or ALT not ≤3 × ULN in 4 weeks, permanently discontinue pexidartinib.
	>10 × ULN	• Permanently discontinue pexidartinib. • Monitor liver tests twice weekly until AST or ALT ≤5 × ULN, then weekly until ≤3 × ULN.
Increased ALP[a] and GGT	ALP >2 × ULN with GGT >2 × ULN	• Permanently discontinue pexidartinib. Monitor liver tests twice weekly until ALP ≤5 times ULN, then weekly until ≤2 × ULN.
Increased bilirubin	TB >ULN to <2 × ULN or DB >ULN and <1.5 × ULN	• Withhold and monitor liver tests twice weekly. • If an alternate cause for increased bilirubin is confirmed and bilirubin <ULN within 4 weeks, resume at reduced dose. • If bilirubin not <ULN in 4 weeks, permanently discontinue pexidartinib.
	TB ≥2 × ULN or DB >1.5 × ULN	• Permanently discontinue pexidartinib. • Monitor liver tests twice weekly until bilirubin ≤ULN.
Adverse Reactions or Other Laboratory Abnormalities		
Any	Severe or intolerable	• Withhold until improvement or resolution. • Resume at a reduced dose upon improvement or resolution.

ALT = alanine aminotransferase; ALP = alkaline phosphatase; AST = aspartate aminotransferase; DB = direct bilirubin; GGT = gamma-glutamyl transferase; TB = total bilirubin; ULN = upper limit of normal.
[a] Confirm ALP elevations as liver isozyme fraction.
Source: Pexidartinib Study Manual

Table 6.4: Additional Liver Evaluation

Evaluation*	Comments
Increase frequency of testing liver chemistries to twice per week, including INR and albumin, and continue until liver chemistries have stabilized, and then reduce to weekly until liver chemistries return to normal or baseline	Investigational treatment may be started after liver function tests recover to Grade 0 to 1 or baseline level, and in consultation with Medical Monitor
Detailed history focusing on medications and substances used: alcohol, change in medication dosages, new medications added, attention to use of acetaminophen, OTC medication use and recreational drug use. Check for change in diet or use of dietary supplements, with particular attention to dose and duration of any herbal product	Suspect medications will be discontinued or substituted for if possible
Detailed medical history and physical exam seeking new abnormalities	Evaluate abnormalities found

Evaluation*	Comments
Full serological evaluation for hepatitis A, B, C and E (IgG and IgM). Check for autoimmune hepatitis with serological laboratory studies	If viral hepatitis or autoimmune hepatitis suggested, have subject evaluated by hepatologist
Liver ultrasound performed to evaluate liver and biliary tree	Evaluate any abnormalities found
Check history for exposure to chemical agents	Remove chemical exposure and have subject seen by hepatologist
Obtain hepatology consult if liver function continues to rise beyond 14 days	Contact Medical Monitor

Ig = immunoglobulin; INR = international normalized ratio; OTC = over-the-counter.
*Cases are to be discussed with the Medical Monitor whenever investigational product is being held for liver function test abnormality.

All dose modifications (interruption, delay, reduction, and/or discontinuation) should be based on the worst preceding toxicity (National Cancer Institute-Common Terminology Criteria for Adverse Events [NCI-CTCAE] version 5.0) as shown in Table 6.3. Dose increases are not permitted for pexidartinib. Dose modification decisions may be based on laboratory results.

Once the dose of pexidartinib has been reduced because of toxicity, all subsequent cycles should be administered at that lower dose level unless further dose reduction is required. More than 2 dose reductions are not allowed and if toxicity continues after 2 dose reductions, the subject will be withdrawn from the study treatment if further toxicity meeting the requirement for dose reduction occurs.

For Grade 3 or Grade 4 events, monitoring (including local laboratory tests when appropriate) should be performed frequently and at an interval no greater than 7 days until the AE is determined to be resolving.

6.5.1. Renal Impairment

A reduced dose of 600 mg/day (200 mg in the morning and 400 mg in the evening) is recommended in study subjects with mild to severe renal impairment (creatinine clearance [CrCL] 15 to 89 mL/min estimated by Cockcroft-Gault using actual body weight).

6.6. Prior and Concomitant Medications

During the study, if the use of any concomitant treatment becomes necessary (e.g., for treatment of an AE), the treatment must be recorded on the source document and 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 30 days of the Baseline visit will be recorded on the eCRF. Note that vaccinations for COVID-19 are to be recorded on the source document and captured on the eCRF under both the concomitant medications section and on the COVID-19 forms.

6.6.1. Analgesic Use

Analgesic use, both prescription and OTC, will be collected in the eCRF in the same manner as other concomitant medications.

6.7. Prohibited Therapies/Products

Subjects enrolled in studies with pexidartinib who are also receiving concomitant warfarin should have their anti-coagulation status carefully monitored, especially shortly after initiation of pexidartinib, for the potential need for adjustments in warfarin dosing. In particular, 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.

Although pexidartinib does not appear to inhibit CYP drug-metabolizing enzymes to an important extent, caution is warranted when administering pexidartinib to subjects taking drugs that are highly dependent on CYP for metabolism and have a narrow therapeutic index. It is not known whether systemic exposure to these medications will increase while subjects are receiving pexidartinib.

Of the 5 major CYP isoforms, 3A4 (BFC) may be involved in Phase 1 metabolism of pexidartinib, with possibly CYP1A2 playing a minor role. Concomitant use of strong CYP3A4 inhibitors (Table 10.2) and inducers should be administered with caution, in the event they alter the systemic exposure to pexidartinib. In general, strong inhibitors or inducers of CYP3A4 should be avoided unless clinically necessary. These include anticonvulsants, certain mycin antimicrobials, and antiretrovirals.

Restricted Therapies/Products

If concomitant use with a strong CYP3A inhibitor (Table 10.2) or UGT inhibitor cannot be avoided, reduce the pexidartinib dose according to the recommendations in Table 6.5. If concomitant use of a strong CYP3A inhibitor or UGT inhibitor is discontinued, increase the pexidartinib dose (after 3 plasma half-lives of the 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 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 per day; CYP = cytochrome P450; UGT = uridine 5'-diphospho-glucuronosyltransferase

6.7.1. Hormonal Contraceptives

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

6.7.2. Acid-reducing Agents

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

Permitted Therapies/Products

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

- Palliative radiation to non-measurable lesion is permitted as long as the radiation field does not include measurable lesion;
- Investigators' discretion is recommended for the following:
  - Prophylactic or supportive treatment for expected toxicities, including management of study drug will be as per Investigator's discretion.

7. STUDY DRUG DISCONTINUATION AND DISCONTINUATION FROM THE STUDY

This section describes subjects who discontinue pexidartinib treatment as part of this study for reasons listed below and **NOT** subjects who are participating in the Treatment-Free period of the **Treatment-Free/Re-Treatment Cohort**.

7.1. Subject Withdrawal/Discontinuation from the Study

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

- Completed
- Complete Response
- Death
- Adverse Event
- Progressive Disease
- Clinical Progression
- Lack of Efficacy
- Withdrawal by Subject (to discontinue study drug)
- Physician Decision
- Lost to Follow-up (see Section 7.2 for details on when a subject is considered Lost to Follow-up)
- Pregnancy
- Protocol Deviation
- Study Termination by Sponsor
- Other

If the reason for study discontinuation is the death of the subject, the options for categorizing the primary cause of death are progressive disease or adverse event. If reason of death is unknown, every effort should be made to obtain the primary cause of death. Only 1 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 (i.e., 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 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;
- If 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 Schedule of Events (Section 1.3) for data to be collected at the time of study discontinuation and for any further evaluations that need to be completed.

7.2. Lost to Follow-up

A subject will be considered lost to follow-up if he/she fails to return for 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, multiple 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, site personnel must make every effort to collect survival status from public records (e.g., obituaries, death certificates, etc.) in accordance with local laws.

8. STUDY PROCEDURES

See Schedule of Events (Section 1.3) for Screening, Baseline, Treatment, and EOS/EOT Follow-up study procedures.

8.1. Eligibility Assessment

Review the subject's demographics, medical and target disease history (if permitted via the subjects signed ICF, these may be transferred from their prior study records), vital signs, and results of tests (e.g., physical examination, ECG, laboratory assessments) and compare against the eligibility criteria (Section 5.1 and Section 5.2).

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.

Tenosynovial Giant Cell Tumor History

Subject's TGCT history will be obtained by the Investigator or a qualified designee. This may be obtained from the subject's file from the prior study.

General Medical History and Baseline Conditions

Subject's medical history will be obtained by the Investigator or a qualified designee.

This may be obtained from the subject's file from the prior study (e.g., the concomitant medications taken during the course of the preceding study will be recorded under prior medications in PL3397-A-U4003). Untoward medical occurrences (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 consent date 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 before 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; which, if permitted via the subjects signed ICF, may be transferred from the subject's file from their prior study, against the eligibility criteria.

8.2. Enrollment

Once a subject has been deemed eligible as per Section 5.1 and Section 5.2, the subject should be enrolled into this study. For subjects choosing to continue treatment with pexidartinib, they will remain on their dosage level at the end of the prior study. For subjects choosing to enroll into the

Treatment-Free period of the **Treatment-Free/Re-Treatment Cohort**, pexidartinib treatment should be immediately stopped.

8.3. Efficacy Assessments

8.3.1. Response Assessment

Assess the subject based upon the local laboratory results using the Response Criteria (Section 10.4). Additional details will be available in the Study Laboratory Manual.

8.3.2. Patient Reported Outcomes

The PROMIS PF (Section 10.6.1) and EQ-ED-5L (Section 10.6.3) questionnaires will be used for PROs.

8.3.3. Radiographic Tumor Assessments

The Investigator will evaluate the MRI scans in order to perform a qualitative tumor assessment (i.e., stable disease). These data will be used to inform the Investigator and patient regarding the next steps in the course of treatment.

The Sponsor may retain the MRI scans to retrospectively evaluate the tumor response, by central radiographic readers, for study and non-study related purposes.

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

- Complete response: Lesion completely gone.
- Partial response: ≥50% decrease in volume score relative to baseline.
- Progressive disease: ≥30% increase in volume relative to lowest score during the study whether at baseline or some other visit.
- Stable disease: Does not meet any of the prior criteria based on score during study.

The cutoffs of 50% for partial response (PR) and ≥30% for progressive disease (PD) were developed in consultation with clinical experts.

The 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 Magnetic Resonance Imaging (RAMRIS), originally developed for rheumatoid arthritis,[8] and Whole-Organ Magnetic Resonance Imaging Score (WORMS), originally developed for osteoarthritis.[9] 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.

Re-Treatment Assessment

At each visit, subjects who are in the Treatment-Free period will be assessed by the Investigator for pexidartinib re-treatment based on Investigator and subject's discretion.

8.4. Safety Assessments

8.4.1. Adverse Event

Methods to Detect Adverse Events

The definitions of an AE, TEAE, and SAE can be found in Section 9.5.2 and Section 10.5. Adverse events 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. Between scheduled clinic visits, subjects should be instructed to enter all AEs in their Diary. 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 (i.e., 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.

COVID-19 assessments are detailed in Section 8.4.4.

Time Period for Collecting Adverse Events, Serious Adverse Events

All serious adverse events (SAEs) occurring after the subject signs the ICF and up to 30 days after the last dose of study medication if applicable or EOS/FU visit, whether observed by the Investigator or reported by the subject, will be recorded on the AE 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 taken the first dose of study medication/signs the ICF until 30 days after the last dose of study medication will be recorded on the AE 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 AE eCRF, unless it is a condition of TGCT.

Reporting Procedure for Investigators

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

Disease progression/worsening of TGCT will not be recorded as an AE on the Adverse Event eCRF. However, events associated with disease progression, 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 SAVER (Serious Adverse Event Report) form within 24 hours of awareness:

- SAEs (Section 10.5.2)
- 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 (as defined in 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 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 or CRO using the provided fax transmittal form and the appropriate fax number provided for the 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 *PL3397-A-U4003 Study Site Manual*) or 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/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 inform Investigators and regulatory authorities of all SAEs, regardless of relatedness, reported from this study, and any Suspected Unexpected Serious

Adverse Event Reactions (SUSARs) occurring in other studies of pexidartinib, as appropriate per institutional/local reporting requirements.

Sponsor 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 pexidartinib IB.[6]

Follow-up for AEs and SAEs

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 Sponsor or CRO 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 **Sponsor and/or CRO** within 24 hours of awareness. Overdose will be reported via the **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.

Occupational exposures must be reported via the SAVER form.

8.4.1.2. Adverse Events of Special Interest

Pexidartinib can cause serious and potentially fatal liver injury. Hepatotoxicity with ductopenia and cholestasis occurred in patients treated with pexidartinib. Across 768 patients who received pexidartinib in clinical trials, there were 2 irreversible cases of cholestatic liver injury. One patient died with advanced cancer and ongoing liver toxicity and 1 patient required a liver transplant. The mechanism of cholestatic hepatotoxicity is unknown and its occurrence cannot be predicted.

It is unknown whether liver injury occurs in the absence of increased transaminases. Avoid pexidartinib in patients with pre-existing increased serum transaminases; total bilirubin or direct bilirubin (>ULN); or active liver or biliary tract disease, including increased ALP. Taking pexidartinib with food increases drug exposure by 100% and may increase the risk of hepatotoxicity. Administer pexidartinib on an empty stomach, at least 1 hour before or 2 hours after a meal or snack. Monitor liver tests, including AST, ALT, total bilirubin, direct bilirubin, ALP and GGT, prior to initiation of pexidartinib, and as defined within the appropriate SoE for the cohorts (Section 1.3). Withhold and dose reduce, or permanently discontinue pexidartinib based on the severity of the hepatotoxicity (Table 6.3).

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 TBIL >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. 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 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 discontinues study drug due to liver enzyme abnormalities, the subject will have additional clinical and laboratory evaluations as described in Section 10.2 in order to determine the nature and severity of the potential liver injury.

Additional information can be found in the *PL3397-A-U4003 Study Manual* and the *Pexidartinib IB*.

8.4.2. Pregnancy/Embryo-Fetal Toxicity

Based on animal studies and its mechanism of action, pexidartinib may cause fetal harm when administered to a pregnant woman. Oral administration of pexidartinib to pregnant rats and rabbits during the period of organogenesis resulted in malformations, increased post-implantation loss, and abortion at exposures approximately equal to the human exposure at the recommended dose of 800 mg based on area under the curve (AUC).

Advise pregnant women of the potential risk to a fetus. As pexidartinib is a moderate CYP3A4 inhibitor, concurrent administration of pexidartinib with ethinyl estradiol may lead to reduced exposure of ethinyl estradiol. 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).

Sponsor must be notified of any female subject or partner of a male subject who becomes pregnant while receiving or within 30 days of discontinuing pexidartinib.

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 (i.e., 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 females of reproductive potential (as defined in Section 5.1), document the results of a negative serum pregnancy test. A positive pregnancy test at Screening will exclude female subject enrollment. Any females enrolled in the study and receiving pexidartinib who become pregnant must discontinue pexidartinib and communicate this information to the Investigator, and have their pregnancy followed to outcome.

8.4.3. Clinical Laboratory Evaluations

The clinical laboratory tests including hematology, coagulation, serum chemistry, TSH and urinalysis will be performed. De-identified laboratory reports with all local laboratory results from samples collected for hematology, coagulation, serum chemistry, TSH, and urinalysis will be collected on the local laboratory form in EDC to be data entered into the clinical database. Refer to Table 10.1 for the complete list of laboratory parameters. Laboratories parameters from the previous pexidartinib studies may be used at Baseline.

Abnormal laboratory values (NCI-CTCAE Grade 3 or 4) occurring during the clinical study will be followed until repeat test results return to normal (or Baseline), stabilize, or are no longer clinically relevant, as determined by the Investigator. New or worsened clinically relevant abnormalities should be recorded as AEs on the Adverse Event eCRF.

8.4.4. Reporting of Exposure to COVID-19 (SARS-CoV-2)

All confirmed or suspected COVID-19 events must be recorded in the eCRF.

- Subjects who test positive for COVID-19 should be reported as “Confirmed COVID-19” either as an AE or serious adverse event (SAE).

The usual protocol mandated SAE reporting requirements should be followed for confirmed or suspected COVID-19 (or SARS-CoV-2) as done for any other AE, ie, the Investigator should assess whether any seriousness criteria are met per protocol, and appropriate protocol reporting requirements should be followed.

In the event that the Investigator assesses that a COVID-19 case does not meet any seriousness criteria as outlined in the protocol, it should be reported as a non-serious AE in the eCRF.

All study drug interruption or dose reduction or discontinuation due to the COVID-19 event must be recorded on the AE and drug administration eCRFs.

For both serious and non-serious COVID-related AEs, the following information should be provided as applicable:

- Date and laboratory results confirming the COVID-19 diagnosis (including viral antigen test and/or antiviral antibody serological test) in the eCRF.

- Clinical course of the case, including presenting signs, symptoms, exposure, actions taken with the investigational products, medications used for treatment or prophylaxis of COVID-19, and outcome in relevant eCRF (eg, concomitant medication, AE).
- Findings from diagnostic imaging (including computed tomography scan or other chest imaging).

8.4.5. Other Safety

Physical Examinations

A complete physical examination should include a weight measurement and an evaluation of the head, eyes, ears, nose, and throat and the cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurological systems. Any abnormality identified at Baseline should be recorded on the General Medical History and Baseline Conditions eCRF. At subsequent visits (or as clinically indicated), limited, symptom-directed physical examinations should be performed. Changes from Baseline abnormalities should be collected in the subject's study record. New or worsened clinically relevant abnormalities should be recorded as AEs on the Adverse Event eCRF.

Vital Signs

Vital signs will include the measurements of respiratory rate, heart rate, systolic and diastolic blood pressures, temperature, height (may be obtained from subject's prior study file), and body weight [for Screening/Baseline this may be obtained from the subject's prior study]. Vital signs should be taken prior to ECG measurement. Blood pressure and pulse rate will be measured after the subject has rested in a recumbent position for at least 5 minutes and prior to laboratory draws.

Electrocardiograms

12 lead-electrocardiograms (ECGs) will be performed and recorded for every subject at Screening. The ECG will be measured after the subject has rested in a recumbent position for at least 5 minutes and the ECG results will be read locally. At any visit during which a subject exhibits a heart rate ≤50 bpm or other clinical indications for ECG, the ECG will be repeated. Any abnormal finding should be confirmed with a repeated ECG. Abnormal, clinically relevant findings occurring post-baseline will be reported as AEs. Whether or not the measurement is performed, the date the ECG is to be performed, heart rate, PR interval, RR interval, QRS amplitude, QT interval, QTcF interval, and results will be recorded in the eCRF.

8.5. Pharmacokinetic (PK) Assessment(s)

Not applicable.

8.6. Pharmacodynamic Assessment(s)

Not applicable.

9. STATISTICAL CONSIDERATIONS

9.1. General Statistical Considerations

This is a phase 4, multicenter study to evaluate the discontinuation and re-treatment of pexidartinib in subjects with TGCT (PVNS or GCT TS) who were previously treated with pexidartinib in one of the following studies: (PLX108-10 (ENLIVEN), PLX108-01, PL3397-A-A103, and PL3397-A U126). There is no statistical hypothesis for this study. The statistical analysis will be descriptive in nature. No p-values will be reported.

9.2. Statistical Hypothesis

Not applicable.

9.3. Sample Size Determination

The study sample size is not based on statistical consideration. Subjects currently enrolled in Studies PLX108-10 (ENLIVEN), PLX108-01, PL3397-A-A103, and PL3397-A-U126 who are eligible can participate in this study.

9.4. Population for Analysis Sets

Analysis Sets

- The Safety Analysis Set will include all subjects who entered this study. Subjects will be analyzed according to their cohort (**Treatment-Free/Re-Treatment Cohort**; **Treatment Continuation Cohort**).
- The Full Analysis Set (FAS) for the **Treatment-Free/Re-Treatment Cohort** will include all subjects who entered the Treatment-Free/Re-Treatment Cohort. This data set will be the primary population for the primary endpoint.
- The Full Analysis Set (FAS) for the **Treatment Continuation Cohort** will include all subjects who entered the Treatment Continuation Cohort.
- The Evaluable Analysis Set (EAS) will include all subjects who entered the study with Baseline measure and at least 1 post-baseline measures available. The data set will be used for PRO measures.
- The Re-Treatment Analysis Set (RAS) will include all subjects who received at least 1 dose of pexidartinib in the **Treatment-Free/Re-Treatment Cohort** after stopping pexidartinib. The data will be used for both efficacy and safety analyses for re-treated subjects in the **Treatment-Free/Re-Treatment Cohort**.

9.5. Statistical Analysis

The Statistical Analysis Plan (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 and secondary endpoints.

9.5.1. Efficacy Analyses

Table 3.1 and Table 3.2 list the primary and secondary endpoints and their corresponding definitions of all endpoints. Additional details for the analysis and censoring rules are noted in the following sections. Detailed censoring rules for the primary and applicable secondary efficacy endpoints will be specified in the SAP.

9.5.1.1. Primary Efficacy Analyses

The primary endpoint in this study is the proportion of subjects who remain treatment-free at Month 12 and Month 24 after entering the Treatment-Free period in the **Treatment-Free/Re-Treatment Cohort**. The primary efficacy analysis will be based on the data from the FAS.

Kaplan-Meier methods will be used to estimate the proportion of subjects who remain treatment-free at Month 12 and Month 24. Estimate of the proportion will be provided with its 95% confidence interval (CI) using Greenwood's formula.

The subjects who resume pexidartinib treatment or died will be considered as an event. The subjects who take subsequent systemic therapy or undergo surgery for the treatment of TGCT will also be counted as an event. The subjects who withdraw consent or lost to follow up with be censored at the last contact date**.**

9.5.1.2. Secondary Efficacy Analyses

The PRO measures will be summarized descriptively over time along with its 95% CI by each cohort. The mean change from Baseline for these measures will also be reported over time along with its 95% CI by each cohort. The analysis will be conducted in the Evaluable Analysis Set (EAS).

Similar analyses will be conducted in the Re-treatment Analysis Set subjects (RAS). In this analysis, the Baseline measure of the retreated subjects is defined as the latest measure prior to or on the date of re-treatment of pexidartinib.

Qualitative assessments of the tumor will be summarized descriptively for pexidartinib re-treated subjects in the **Treatment-Free/Re-Treatment Cohort** and for all subjects in the **Treatment Continuation Cohort.**

9.5.1.3. Exploratory Analyses

Exploratory analysis will be descriptive only. Details of the exploratory analysis will be specified in the SAP.

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 by cohort separately.

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 30 days after last dose of study drug. AEs collected after 30 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. Incidence of TEAEs occurring over time, (e.g., 0 to 6 months, 6 to 12 months, etc.) will be summarized. The number and percentage of subjects reporting TEAEs will be calculated overall, by system organ class, by preferred term, and by cohort.

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, and TEAEs leading to 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. AEs due to COVID-19 will be also summarized and listed.

Clinical Laboratory Evaluation

Descriptive statistics will be provided for the clinical laboratory results by scheduled time of evaluation and by cohort, 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 EOT visit.

Abnormal clinical laboratory results will be graded according to NCI-CTCAE version 5.0, if applicable, and the grade will be presented in a by-subject data listing. A shift table, presenting by cohort 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.

ECG

Descriptive statistics will be provided for the ECG measurements by scheduled time of evaluation and by cohort, 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 ECG data will be generated.

Vital Signs

Descriptive statistics will be provided for the vital sign measurements by scheduled time of evaluation and by cohort, 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 data will be generated.

Other

Listings of all other safety endpoints (e.g., physical examination findings) will be generated.

9.5.3. Other Analyses

No other analyses are planned in this study.

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 (e.g., 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 IRB or IEC 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, IEC, and/or applicable regulatory authorities.

The Investigator should notify the IRB or IEC 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.

The Sponsor will appoint a Coordinating Investigator. Among other possible duties, the Coordinating Investigator will be responsible for reviewing the Final Clinical Study Report and testifying to the accuracy of the description of the study conduct. Because the Coordinating Investigator should have personal knowledge of the conduct of the study, he or she will normally be chosen from among those Investigators who have enrolled and treated at least 1 subject. However, where an Investigator has special knowledge of the field or of the study, the Coordinating Investigator can be chosen prior to enrollment of the first subject. In all cases, the Coordinating Investigator must be chosen prior to locking the database.

Compliance Statement, Ethics, and Regulatory Compliance

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

- European Commission Directive (2001/20/EC Apr 2001) and/or;
- European Commission Directive (2005/28/EC Apr 2005) and/or;
- US Food and Drug Administration (FDA) GCP Regulations: Code of Federal Regulations (CFR) Title 21, parts 11, 50, 54, 56 and 312 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(s), and of any suspected/actual serious GCP non-compliance brought to the attention of the Investigator.

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, ECs/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 EC/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 EC/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 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.

For study sites in the US, an additional consent is required for the Health Insurance Portability and Accountability Act (HIPAA).

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 Sponsor will observe the rules laid down in the European Data Protection Directive 95/46/EC and General Data Protection Regulation 2016/679 on the protection of individuals with regard to the processing of personal data and the free movement of such data.

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 (e.g., 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 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 (e.g., 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 *PL3397-A-U4003 Study 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 (e.g., 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 Sponsor or 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 such as local laboratories will be entered into the clinical database.

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

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

10.1.5. Committees

Not applicable.

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 (i.e., there is no other written or electronic record of data). In this study, eCRFs may be used as source documents.

Records of subjects, source documents, monitoring visit logs, data correction forms, eCRFs, inventory of study drug, regulatory documents (e.g., 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 site personnel 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 2 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 2 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 the Sponsor. 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 and Public Disclosure Policy

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 participating country 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 disclosure) based on data generated in this study must be reviewed and approved in writing by the Sponsor prior to submission.

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 (e.g., inclusion/exclusion criteria, dosing, missed study visits) within 24 hours of knowledge and 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 1 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

Study termination may also be requested by (a) competent authority/ies.

10.1.11. Product Complaints

A product complaint is any dissatisfaction with a product that may be attributed to the identity, quality, durability, reliability, or safety of the product. Individuals who identify a potential product complaint situation should immediately report the event. Whenever possible, the associated product should be maintained in accordance with the label instructions pending further guidance from a quality representative form the Sponsor.

For product complaints, refer to the *PLX3397-A-U4003 Pharmacy Manual* for instructions and details.

10.2. Appendix 2: Laboratory Assessments

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 albumin globulin (A/G) ratio (optional) alanine aminotransferase (ALT) alkaline phosphatase (ALP) aspartate aminotransferase (AST) bilirubin (total) bilirubin (direct) blood urea nitrogen (BUN)/urea calcium (Ca) chloride (Cl) creatinine cholesterol (total) creatinine clearance (Cockcroft-Gault Equation)	creatine phosphokinase (CPK) gamma-glutamyl transaminase (GGT) glucose (fasting) lactate dehydrogenase lipase lipoprotein, high density/HDL-cholesterol lipoprotein, low density/LDL-cholesterol magnesium (Mg) phosphorus potassium (K) protein (total) sodium (Na) triglycerides uric acid
Hematology	hemoglobin hematocrit platelet count red blood cell (RBC) count white blood cell (WBC) count	differential WBC count: basophils eosinophils lymphocytes monocytes neutrophils
Coagulation	prothrombin time (PT)- international normalized ratio (INR) activated partial thromboplastin time (aPTT) optional: partial thromboplastin time (PTT) if aPTT is not collected	
Urinalysis (abbreviated)	bilirubin glucose ketone bodies occult blood pH protein	urobilinogen sediments: casts RBC WBC
Hormone testing	Follicular Stimulating Hormone (FSH) (females only) Thyroid Stimulating Hormone (TSH)	Baseline and BL-2 only

10.3. Appendix 3: Reference Standards

10.3.1. Cockcroft-Gault Equation

The estimated creatinine clearance (CrCL; mL/min) will be calculated using the Cockcroft-Gault equation based on [actual/ideal] weight in kilograms (1 kilogram = 2.2 pounds):[10]

Conventional – serum creatinine in mg/dL:

Male:

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

Female:

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

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

Male:

$$\text{CrCL (mL/min)} = \frac{[140 - \text{age (in years)}] \times \text{weight (in kg)}}{\text{serum creatinine (in µmol/L)} \times 72 \times 0.0113}$$

Female:

$$\text{CrCL (mL/min)} = \frac{[140 - \text{age (in years)}] \times \text{weight (in kg)}}{\text{serum creatinine (in µmol/L)} \times 72 \times 0.0113} \times 0.85$$

10.3.2. CYP3A4 Inhibitors and Inducers

Table 10.2 lists the generic names of strong, moderate, and weak CYP3A4 inhibitors.[11] This is not a complete list and information for all non-listed medications should be confirmed against their prescribing information.

Table 10.2: CYP3A4 Inhibitors

Inhibitor Type	Generic Drug Name	Allowance
Strong	boceprevir clarithromycin conivaptan grapefruit grapefruit juice indinavir itraconazole ketoconazole lopinavir mibefradil nefazodone nelfinavir posaconazole ritonavir saquinavir telaprevir telithromycin voriconazole	Use should be avoided if possible. Requires pexidartinib dose reduction.
Moderate	amprenavir aprepitant atazanavir ciprofloxacin crizotinib darunavir diltiazem erythromycin fluconazole fosamprenavir imatinib verapamil	Use allowed. No requirement for pexidartinib dose reduction.

Inhibitor Type	Generic Drug Name	Allowance
Weak	alprazolam amiodarone amlodipine atorvastatin bicalutamide cilostazol cimetidine cyclosporine fluoxetine fluvoxamine ginkgo goldenseal isoniazid lapatinib oral contraceptives nilotinib pazopanib ranitidine ranolazine ticagrelor tipranavir zileuton	Use allowed. No requirement for pexidartinib dose reduction

Adapted from: http://medicine.iupui.edu/clinpharm/ddis/main-table

10.4. Appendix 4: Response Criteria

The Investigator will evaluate the MRI scans to perform a qualitative tumor assessment (i.e., stable disease). These data will be used to inform the Investigator and patient regarding the next steps in course of treatment.

The Sponsor may retain the MRI scans for possible future (not study-related) use to retrospectively evaluate the tumor response (i.e., RECIST) and TVS by central radiographic readers, as outlined in the criteria below.

Response Evaluation Criteria in Solid Tumors (Version 1.1)

Assessment of tumor responses will be performed according to revised RECIST Guidelines, Version 1.1.[13] Some of these definitions and criteria are highlighted below.

Measurability of Tumor at Baseline Definitions

At Baseline, tumor lesions/lymph nodes will be categorized as measurable or non-measurable as follows:

Measurable

Tumor lesions: Must be accurately measured in at least 1 dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:

- 10 mm by computed tomography (CT) scan (CT scan slice thickness no greater than 5 mm)
- 10 mm caliper measurement by clinical examination (lesions which cannot be accurately measured with calipers should be recorded as non-measurable)
- 20 mm by chest X-ray

Measurable malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm in the short axis when assessed by CT scan (CT scan slice thickness is recommended to be no greater than 5 mm). At Baseline and quarterly scans, only the short axis will be measured and followed. See also notes below on "Baseline documentation of target and non-target lesions" for information on lymph node measurement.

Non-measurable

All other lesions, including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥10 to <15 mm short axis) as well as truly non-measurable lesions. Lesions considered truly non-measurable include leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical examination that is not measurable by reproducible imaging techniques.

Special Considerations Regarding Lesion Measurability

Bone lesions, cystic lesions, and lesions previously treated with local therapy require particular comment:

Bone lesions:

- Bone scan, positron emission tomography (PET) scan or plain films are not considered adequate imaging techniques to measure bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.
- Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by cross sectional imaging techniques such as CT or MRI can be considered as measurable lesions if the soft tissue component meets the definition of measurability described above.
- Blastic bone lesions are non-measurable.

Cystic lesions:

- Lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.
- 'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if noncystic lesions are present in the same subject, these are preferred for selection as target lesions.

Lesions with prior local treatment:

- Tumor lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, are not considered measurable unless there has been demonstrated progression in the lesion since the therapy.

Specifications by Methods of Measurements

Measurement of Lesions

All measurements should be recorded in metric notation, using calipers if clinically assessed.

Method of Assessment

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during quarterly scans. Imaging-based evaluation should always be done rather than clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical examination.

CT, MRI: CT is the best currently available and reproducible method to measure lesions selected for response assessment. This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. When CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g., for body scans).

Tumor Response Evaluation

Assessment of Overall Tumor Burden and Measurable Disease

To assess objective response or future progression, it is necessary to estimate the overall tumor burden at Baseline and use this as a comparator for subsequent measurements.

Baseline Documentation of 'Target' and 'Non-Target' Lesions

When more than 1 measurable lesion is present at baseline all lesions up to a total of 2 lesions per organ and a maximum of 5 lesions total representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline (this means in instances where subjects have only 1 or 2 organ sites involved a maximum of 2 and 4 lesions respectively will be recorded).

Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected.

Lymph nodes merit special mention since they are normal anatomical structures which may be visible by imaging even if not involved by tumor. As noted above, pathological nodes which are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of ≥15 mm by CT scan. Only the short axis of these nodes will contribute to the baseline sum. The short axis of the node is the diameter normally used by radiologists to judge if a node is involved by solid tumor. Nodal size is normally reported as two dimensions in the plane in which the image is obtained (for CT scan this is almost always the axial plane; for MRI the plane of acquisition may be axial, sagittal, or coronal). The smaller of these measures is the short axis. For example, an abdominal node which is reported as being 20 mm × 30 mm has a short axis of 20 mm and qualifies as a malignant, measurable node. In this example, 20 mm should be recorded as the node measurement. All other pathological nodes (those with short axis ≥10 mm but <15 mm) should be considered non-target lesions. Nodes that have a short axis <10 mm are considered non-pathological and should not be recorded or followed.

A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then as noted above, only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

All other lesions (or sites of disease) including pathological lymph nodes should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required, and these lesions should be followed as 'present', 'absent', or in rare cases 'unequivocal progression'.

Evaluation of Target Lesions

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm.

Partial Response (PR): At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.

Progressive Disease (PD): At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an

absolute increase of at least 5 mm. (**Note:** the appearance of 1 or more new lesions is also considered progression.)

Stable Disease: Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

Special Notes on the Assessment of Target Lesions

Lymph nodes: Lymph nodes identified as target lesions should always have the actual short axis measurement recorded (measured in the same anatomical plane as the baseline examination), even if the nodes regress to below 10 mm on study. This means that when lymph nodes are included as target lesions, the 'sum' of lesions may not be zero even if CR criteria are met, since a normal lymph node is defined as having a short axis of < 10 mm. For PR, stable disease, and PD, the actual short axis measurement of the nodes is to be included in the sum of target lesions.

Target lesions that become 'too small to measure': All lesions (nodal and non-nodal) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (e.g., 2 mm). However, sometimes lesions or lymph nodes which are recorded as target lesions at baseline become so faint on CT scan that the radiologist may not feel comfortable assigning an exact measure and may report them as being 'too small to measure'. When this occurs, it is important that a value be recorded on the eCRF. If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm. If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned. (**Note:** It is unlikely that this rule will be used for lymph nodes since they usually have a definable size when normal and are frequently surrounded by fat such as in the retro-peritoneum.) This default value is derived from the 5 mm CT slice thickness (but should not be changed with varying CT slice thickness.) The measurement of these lesions is potentially non-reproducible; therefore, providing this default value will prevent false responses or progressions based upon measurement error.

If the Radiologist is able to provide an actual measurement, that should be recorded, even if it is below 5 mm.

Lesions that split or coalesce on treatment: When non-nodal lesions 'fragment', the longest diameters of the fragmented portions should be added together to calculate the target lesion sum. Similarly, as lesions coalesce, a plane between them may be maintained that would aid in obtaining maximal diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the vector of the longest diameter in this instance should be the maximal longest diameter for the 'coalesced lesion'.

Evaluation of Non-Target Lesions

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm short axis).

Non-CR/Non-PD: Persistence of 1 or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

Progressive Disease (PD): Unequivocal progression (see comments below) of existing non-target lesions. (**Note:** the appearance of 1 or more new lesions is also considered progression.

Special Notes on Assessment of Progression of Non-target Disease

The concept of progression of non-target disease requires additional explanation as follows, when the subject also has measurable disease. In this setting, to achieve 'unequivocal progression' on the basis of the non-target disease, there must be an overall level of substantial worsening in non-target disease such that, even in presence of stable disease (SD) or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest 'increase' in the size of 1 or more non-target lesions is usually not sufficient to qualify for unequivocal progression status. The designation of overall progression solely on the basis of change in non-target disease in the face of SD or PR of target disease will therefore be extremely rare.

New Lesions

The appearance of new malignant lesions denotes disease progression; therefore, some comments on detection of new lesions are important. There are no specific criteria for the identification of new radiographic lesions; however, the finding of a new lesion should be unequivocal, i.e., not attributable to differences in scanning technique, change in imaging modality, or findings thought to represent something other than tumor (for example, some 'new' bone lesions may be simply healing or flare of pre-existing lesions). This is particularly important when the subject's baseline lesions show partial or complete response. For example, necrosis of a liver lesion may be reported on a CT scan report as a 'new' cystic lesion, which it is not.

A lesion in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate disease progression. An example of this is the subject who has visceral disease at baseline and while on study has a CT or MRI of the brain which reveals metastases. The subject's brain metastases are considered to be evidence of PD even if he/she did not have brain imaging at baseline.

If a new lesion is equivocal, for example because of its small size, continued therapy and follow-up evaluation will clarify if it represents truly new disease. If repeat scans confirm there is definitely a new lesion, then progression should be declared using the date of the initial scan that indicated its presence.

Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the study treatment until the EOT. Confirmatory measurement for CR or PR is [not] required in this study. The subject's best overall response assignment will depend on the findings of both target and non-target disease and will also take into consideration the appearance of new lesions.

Missing Assessments and In-evaluable Designation

When no imaging/measurement is done at all at a particular time point, the subject is not evaluable (NE) at that time point. If only a subset of lesion measurements is made at an assessment, usually the case is also considered NE at that time point, unless a convincing argument can be made that the contribution of the individual missing lesion(s) would not change the assigned time point response. This would be most likely to happen in the case of PD. For example, if a subject had a baseline sum of 50 mm with 3 measured lesions and at follow-up

only 2 lesions were assessed, but those gave a sum of 80 mm, the subject will have achieved PD status, regardless of the contribution of the missing lesion.

Best Overall Response: All Time Points

The best overall response is determined once all the data for the subject are known.

Best response determination in studies where confirmation of complete or partial response IS NOT required: Best response in these studies is defined as the best response across all time points (for example, a subject who has stable disease at first assessment, PR at second assessment, and PD on last assessment has a best overall response of PR). When stable disease is believed to be best response, it must also meet the protocol specified minimum time from baseline (within 4 weeks prior to the first dose of study drug), 7 weeks, in the case of scan intervals of 8 weeks (or "5 weeks", in the case of scan intervals of 6 weeks.) If the minimum time is not met when stable disease is otherwise the best time point response, the subject's best response depends on the subsequent assessments. For example, a subject who has stable disease at first assessment, PD at second and does not meet minimum duration for stable disease, will have a best response of PD. The same subject lost to follow-up after the first stable disease assessment would be considered NE.

Table 10.3: Best Overall Response When Confirmation of CR and PR Required

Overall response		**Overall response**
First time point	**Subsequent time point**	**Best**
CR	CR	CR
CR	PR	SD, PD or PR[a]
CR	SD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	NE	SD provided minimum criteria for SD duration met, otherwise, PD
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
PR	NE	SD provided minimum criteria for SD duration met, otherwise, PD
NE	NE	NE

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

[a] If a CR is truly met at first time point, then any disease seen at a subsequent time point, even disease meeting PR criteria relative to baseline, makes the disease PD at that point (since disease must have reappeared after CR). Best response would depend on whether minimum duration for SD was met. However, sometimes 'CR' may be claimed when subsequent scans suggest small lesions were likely still present and in fact the patient had PR, not

CR at the first time point. Under these circumstances, the original CR should be changed to PR and the best response is PR.

Source: Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). Table 3. Euro J of Can. 2009:45;228-47

Special Notes on Response Assessment

When nodal disease is included in the sum of target lesions and the nodes decrease to 'normal' size (< 10 mm), they may still have a measurement reported on scans. This measurement should be recorded even though the nodes are normal in order not to overstate progression should it be based on increase in size of the nodes. As noted earlier, this means that subjects with CR might not have a total sum of '0' on the eCRF.

Subjects with a global deterioration of health status requiring discontinuation of pexidartinib without objective evidence of disease progression at that time should be reported as 'clinical progression.' Every effort should be made to document objective progression even after discontinuation of treatment. Symptomatic deterioration is not a descriptor of an objective response: it is a reason for stopping study drug. The objective response status of such subjects is to be determined by evaluation of target and non-target disease. If a radiographic tumor assessment has not been performed within 4 weeks of the time of clinical progression, then another radiographic assessment should be performed without waiting for the next regularly scheduled scan.

For equivocal findings of progression (e.g., very small and uncertain new lesions; cystic changes or necrosis in existing lesions), treatment may continue until the next scheduled assessment. If at the next scheduled assessment, progression is confirmed, the date of progression should be the earlier date when progression was suspected.

Frequency of Tumor Re-evaluation

In this study, tumor measurement will be conducted at Screening, and then at the intervals specified or sooner if clinically indicated. The interval between scans is based on the last scan visit. Tumor measurement will be performed during the EOT visit if it was not done within the previous 8 weeks or the previous assessment demonstrated disease progression.

Baseline tumor assessments must be performed within 4 weeks prior to the first dose of study drug.

All efforts should be made to ensure consistency between the Baseline measurements and all subsequent measurements in reference to utilization of scanning method, equipment, technique (including slice thickness and field of view), and radiographic interpreter.

The radiographic evaluation may include CT or MRI scanning of the chest, abdomen, and pelvis. Any additional suspected sites of disease should also be imaged. All evaluations should meet the standard of care for imaging of lesions in the respective organ(s) and should conform to the image acquisition guidelines according to institutional standards.

All target and non-target sites are evaluated at each time point of tumor assessment.

10.5. Appendix 5: General Information – Adverse Events

10.5.1. 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.[14]

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 (e.g., ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically relevant in the medical and scientific judgment of the Investigator (i.e., 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 (e.g., 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.

10.5.2. Serious Adverse Event

A serious adverse event 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 (e.g., 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.

Events Exempted from SAE Reporting

Serious events that are also efficacy endpoints and/or safety endpoints will be exempted from SAE processing and expedited reporting.[14] Endpoints are captured on designated eCRF. These events are clinically anticipated events in the target treatment population.

10.5.3. 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 (i.e., cannot be life-threatening or fatal), whereas sepsis can only be Grade 4 or 5 (i.e., 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.

10.5.4. Causality Assessment

The Investigator should assess causal relationship between an adverse event 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 (e.g., 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 (e.g., disease under study, concurrent diseases, and concomitant medications).

10.5.5. 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.
- Not Applicable
- Unknown: Subject is lost to follow-up

10.5.6. Other Action Taken for Event

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

10.5.7. 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

10.6. Appendix 7: Patient Reported Outcomes

10.6.1. PROMIS Physical Function Scale

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

Please respond to each item by marking 1 box per row.

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

		Without any difficulty	With a little difficulty	With some difficulty	With much difficulty	Unable to do
PFB1	Does your health now limit you in doing moderate work around the house like vacuuming, sweeping floors or carrying in groceries?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFA5	Does your health now limit you in lifting or carrying groceries?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
		Without any difficulty	**With a little difficulty**	**With some difficulty**	**With much difficulty**	**Unable to do**
PFA21	Are you able to go up and down stairs at a normal pace?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFA42	Are you able to carry a laundry basket up a flight of stairs?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFA10	Are you able to stand for one hour?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
		Not at all	**Very little**	**Somewhat**	**Quite a lot**	**Cannot do**
PFA3	Does your health now limit you in bending, kneeling, or stooping?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
		Without any difficulty	**With a little difficulty**	**With some difficulty**	**With much difficulty**	**Unable to do**
PFA13	Are you able to exercise for an hour?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1

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

Please respond to each item by marking 1 box per row.

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

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

10.6.3. EQ-5D-5L

Health Questionnaire

English version for the USA

1

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

MOBILITY

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

SELF-CARE

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

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

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

PAIN / DISCOMFORT

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

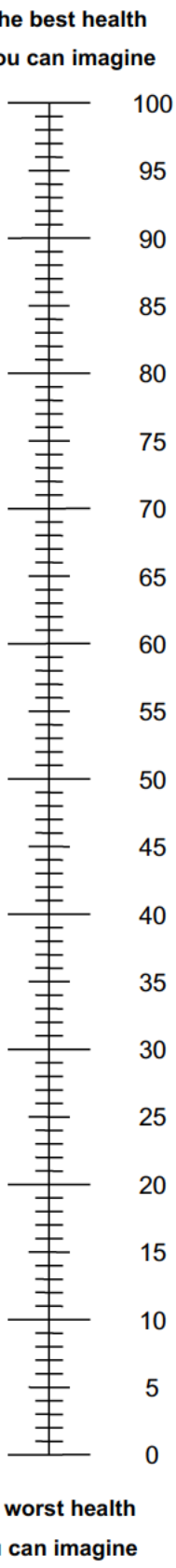
ANXIETY / DEPRESSION

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

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

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

YOUR HEALTH TODAY = ☐



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12. LIST OF ABBREVIATIONS

Abbreviation	Definition
ADR	adverse drug reaction
AE	adverse event
AESI	adverse event of special interest
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AML	acute myeloid leukemia
ASCO	American Society of Clinical Oncology
AST	aspartate aminotransferase
AUC	area under the curve
BID	twice a day
CI	confidence interval
CFR	code of federal regulations
CR	complete response
CrCl	creatinine clearance
CRF	case report form
CRO	contract research organization
CSF1R	Colony stimulating factor 1 receptor
CSF1	Colony stimulating factor 1
CT	computed tomography
CTC	common toxicity criteria
CTCAE	common terminology criteria for adverse events
CYP	cytochrome P450
DMC	data monitoring committee
DSI	Daiichi-Sankyo, Inc.
EAS	evaluable analysis set
EC	ethics committee
ECI	event of clinical interest
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture
EIU	exposure in utero
EOS	End of Study

Abbreviation	Definition
EOT	End of Treatment
EQ-5D-5L	European Quality of Life Five Dimension Five Level Scale
EU	European Union
FAS	full analysis set
FDA	Food and Drug Administration
FMS	feline McDonough sarcoma
FSH	follicle stimulating hormone
GCP	good clinical practice
GCT-TS	giant cell tumor of the tendon sheath [
GGT	gamma-glutamyl transferase
GI	gastrointestinal
GISTs	Gastrointestinal stromal tumors
H2	histamine 2
HIPAA	health insurance portability and accountability act
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Conference on Harmonisation
ICMJE	International Council of Medical Journal Editors
IEC	independent ethics committee
INN	international non-proprietary name
INR	international normalized ratio
IRB	institutional review board
LFT	liver function test
M-CSF	macrophage-colony stimulating factor
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
NCI	National Cancer Institute
NCI-CTCAE	National Cancer Institute – Common Terminology Criteria for Adverse Events
NE	not evaluable
ORR	overall response rate
OS	overall survival
OTC	over-the-counter
PET	positron emission tomography
PD	progressive disease

Abbreviation	Definition
PFS	progression-free survival
PR	partial response
pRBC	packed red blood cell
PPI	proton pump inhibitors
PROs	patient reported outcomes
PROMIS PF	Patient-Reported Outcomes Measurement Information System – Physical Function
PVNS	pigmented villonodular synovitis
QTc	corrected QT interval
QTcF	QT interval corrected with Fridericia's formula
RAMRIS	Rheumatoid Arthritis Magnetic Resonance Imaging
RAS	re-treatment analysis set
RECIST	response evaluation criteria in solid tumors version 1.1
RES	response evaluable set
SAE	serious adverse event
SAP	statistical analysis plan
SAVER	Serious Adverse Event Report
SCF	stem cell growth factor
SCR	Screening
SD	stable disease
SID	subject identifier
SOC	system organ class
SoE	Schedule of Events
SOP	Standard Operating Procedure
SUSAR	suspected unexpected serious adverse reaction
TAMs	Tumor-associated macrophages
TBIL	total bilirubin
TEAE	treatment-emergent adverse event
TGCT	Tenosynovial giant cell tumor
TVS	tumor volume score
UGT	Uridine 5'-diphospho-glucuronosyltransferase
ULN	upper limit of normal
US	United States
WHO	World Health Organization

Abbreviation	Definition
WHODD	World Health Organization Drug Dictionary
WORMS	Whole-Organ Magnetic Resonance Imaging Score

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