Protocol ID: DCC-3014-03-001

Official Title: A Phase 3, Randomized, Placebo-controlled, Double-blind Study of Vimseltinib to Assess the Efficacy and Safety in Patients With Tenosynovial Giant Cell Tumor (MOTION)

NCT Number: NCT05059262

Protocol Approval Date: 31 May 2023

CLINICAL STUDY PROTOCOL

Vimseltinib (DCC-3014)

DCC-3014-03-001

A Phase 3, Randomized, Placebo-controlled, Double-blind Study of Vimseltinib to Assess the Efficacy and Safety in Patients with Tenosynovial Giant Cell Tumor (MOTION)

Study Sponsor: Deciphera Pharmaceuticals, LLC

200 Smith Street
Waltham, MA 02451
Phone: 781-209-6400

IND Number: 131218

NCT Number: NCT05059262

EudraCT Number: 2020-004883-25

Version (Date): Amendment 3 (31 May 2023)

Amendment 2.2 (21 Jun 2022, Canada-specific)

Amendment 2 (07 Mar 2022)

Amendment 1 (11 Feb 2021)

Original (15 Dec 2020)

This study will be conducted according to the protocol and in compliance with Good Clinical Practice, the ethical principles stated in the Declaration of Helsinki, and other applicable regulatory requirements.

2. SYNOPSIS

Name of Sponsor: Deciphera Pharmaceuticals, LLC
Name of Active Ingredient: Vimseltinib (DCC-3014)
Title: A Phase 3, Randomized, Placebo-controlled, Double-blind Study of Vimseltinib to Assess the Efficacy and Safety in Patients with Tenosynovial Giant Cell Tumor (MOTION)
Phase of Development: 3
Planned Number of Study Sites: Approximately 45 centers globally
Planned Number of Participants: Approximately 120 participants
Primary Objective: • To evaluate anti-tumor activity of vimseltinib using Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 by blinded independent radiological review (IRR) **Secondary Objectives:** • To assess anti-tumor activity of vimseltinib using tumor volume score (TVS) and modified RECIST (mRECIST) by blinded IRR • To assess the effects of vimseltinib on range of motion (ROM) • To assess the effects of vimseltinib on physical function, worst stiffness, worst pain, and quality of life (QoL) using patient-reported outcome (PRO) measures • To assess safety and tolerability of vimseltinib Exploratory objectives are listed in Section 6.1.
Primary Endpoint: • Objective response rate (ORR, including complete response [CR] and partial response [PR]) per RECIST v1.1 at Week 25 **Key Secondary Endpoints:** • ORR per TVS at Week 25 • Change from baseline in active ROM of the affected joint, relative to a reference standard, at Week 25 • Change from baseline in the Patient-reported Outcomes Measurement Information System (PROMIS) Physical Function score at Week 25 • Change from baseline in the Worst Stiffness numeric rating scale (NRS) score at Week 25 • Change from baseline in EQ-VAS (EuroQol Visual Analogue Scale) at Week 25 • Response of at least a 30% improvement in the mean Brief Pain Inventory (BPI) Worst Pain NRS score without a 30% or greater increase in narcotic analgesic use at Week 25 **Other Secondary Endpoints:** • ORR per RECIST v1.1

- ORR assessed by mRECIST at Week 25
- Duration of response (DOR; time from first PR or CR to disease progression or death) assessed using RECIST v1.1, TVS, and mRECIST
- Incidence of treatment-emergent adverse events (TEAEs), treatment-emergent serious adverse events, related TEAEs, dose reductions, dose interruptions, and discontinuation of study drug due to adverse event
- Changes from baseline in laboratory parameters, electrocardiograms (ECGs), and vital signs

Exploratory endpoints are listed in Section 6.2.

Study Design: This is a multicenter, randomized, placebo-controlled study of vimseltinib in patients with tenosynovial giant cell tumor (TGCT), consisting of 2 parts: Part 1 is double-blinded and Part 2 is open label. Symptomatic patients with histologically confirmed TGCT for whom surgical resection will potentially cause worsening functional limitation or severe morbidity will be eligible. Patients who received anti-colony-stimulating factor 1/colony-stimulating factor 1 receptor (CSF1/CSF1R) therapy previously (except for imatinib or nilotinib) will be excluded. The study will evaluate efficacy, safety, clinical outcome assessments, pharmacokinetics (PK), and pharmacodynamics of vimseltinib in this population.

The study will consist of a 42-day screening period prior to the first dose of study drug, a Part 1 double-blinded treatment period of 24 weeks (referred to in 28-day cycles) and a Part 2 open-label period until Week 49. Participants will continue treatment after Week 49 during the extension period. There will also be an End-of-Treatment (EOT) Visit within 7 days after the decision to stop study drug, a Safety Follow-up Visit 30 days (±5 days) after the last dose of study drug, and a Disease Follow-up period of up to 2 years or until initiation of new TGCT treatment or surgery, whichever occurs first. Participants will be allowed to undergo surgical resection only after completion of Part 1.

Approximately 120 participants will be randomized in a 2:1 ratio to receive either vimseltinib at the dose of 30 mg twice weekly (biw) (n=80) or placebo (n=40) for 24 weeks. Randomization will be stratified for tumor location (lower limb/all other) and region (U.S./non-U.S.).

At Week 25, the primary and secondary endpoints will be assessed, and participants randomized to placebo in Part 1 will have the option to crossover and receive open-label vimseltinib in Part 2 upon completion of Part 1. Participants randomized to placebo in Part 1 with confirmed disease progression by blinded IRR before Week 25 are eligible for early entry into Part 2. Participants randomized to vimseltinib in Part 1 with confirmed disease progression by IRR before Week 25 will discontinue from study, while those without confirmed disease progression by IRR before Week 25 will continue to receive vimseltinib in Part 2 upon completion of Part 1.

Anti-tumor activity will be assessed by RECIST v1.1. Tumor volume score and mRECIST will be used as additional assessments of anti-tumor activity. Range of motion assessments will be performed and PRO measures will be collected. Safety will be assessed using Common Terminology Criteria for Adverse Events (CTCAE) v5.0. Correlation between efficacy or safety with PK and pharmacodynamics will be explored.

Duration of Treatment: Participants will be eligible to receive study drug until radiological confirmation of disease progression (refer to Section 10.5), unacceptable toxicity, withdrawal by participant, physician's decision, or commercial availability of vimseltinib, and for as long as vimseltinib is being developed to support the indication, and continuation of treatment does not conflict with the Sponsor's right to terminate the study.

Inclusion Criteria: Participants must meet all of the following criteria to be eligible to enroll in the study.

1. Male or female participants ≥18 years of age
2. Histologically confirmed diagnosis of TGCT (formerly known as pigmented villonodular synovitis [PVNS] or giant cell tumor of the tendon sheath [GCT-TS]). Tumor biopsy to confirm TGCT diagnosis will be required if no histology/pathology is available
    a. Participants should have TGCT in a single joint and must have TGCT in joints where ROM assessments can be assessed
3. Disease for which surgical resection will potentially cause worsening functional limitation or severe morbidity as judged by surgical consultation or a multidisciplinary tumor board
4. Symptomatic disease with at least moderate pain or at least moderate stiffness (defined as a score of 4 or more, with 10 describing the worst condition) within the screening period and documented in the medical record
5. Participants should complete 14 consecutive days of questionnaires during the screening period and must meet minimum requirements outlined in Table 4
6. An analgesic regimen, if used, needs to be stable (ie, no change in dose) as judged by the Investigator for at least 2 weeks prior to the first dose of study drug
7. Measurable disease per RECIST v1.1 with at least one lesion having a minimum size of 2 cm, as assessed from magnetic resonance imaging (MRI) scans by a central radiologist
8. Adequate organ function and bone marrow reserve as indicated by the following laboratory assessments performed within 21 days prior to the first dose of study drug:
    a. Bone marrow function: absolute neutrophil count (ANC) ≥1500/μL; hemoglobin ≥10 g/dL; platelet count ≥lower limit of normal (LLN)
    b. Hepatic function: total serum bilirubin ≤upper limit of normal (ULN); serum aspartate aminotransferase (AST)/alanine aminotransferase (ALT) ≤ULN
    c. Renal function: creatinine clearance ≥50 mL/min based either on urine collection or Cockcroft-Gault estimation
    d. Electrolytes ≥LLN for: potassium, magnesium, and calcium
9. Able to take oral medication
10. Participants of reproductive potential must:
    a. Have a negative serum beta-human chorionic gonadotropin (β-hCG) pregnancy test at screening (female participants)
    b. Agree to follow the contraception requirements outlined in the protocol
11. The participant is capable of understanding and complying with the protocol and has signed the informed consent form (ICF). A signed ICF must be obtained before any study-specific procedures are performed
12. Willing and able to complete the PRO assessments on an electronic device

Exclusion Criteria: Participants meeting any of the following criteria will be excluded from the study.

1. Previous use of systemic therapy (investigational or approved) targeting CSF1 or CSF1R including vimseltinib; previous therapy with imatinib and nilotinib is allowed
2. Treatment for TGCT, including investigational therapy, during the screening period

   NOTE: Participants may not be part of an ongoing or have prior participation in a non-TGCT investigational drug study within 30 days of screening. Ongoing participation in a noninterventional study (including observational studies) is permitted.
3. Known metastatic TGCT or other active cancer that requires concurrent treatment (exceptions will be considered on a case-by-case basis depending on tumor type, stage, location, planned treatment, and expected recovery after discussion and approval by Sponsor)
4. Baseline prolongation of the QT interval corrected by Fridericia's formula (QTcF) based on repeated demonstration of QTcF >450 ms in males or >470 ms in females or history of long QT syndrome
5. Receive concurrent treatment with any prohibited medications
   - Acetaminophen usage exceeding 3 g/day
   - Proton-pump inhibitors taken within 4 days prior to the first dose of study drug
   - Medications that are breast cancer resistance protein (BCRP) or organic cation transporter 2 (OCT2) substrates taken within at least 4 days or 5×half-life (whichever is longer) prior to the first dose of study drug
   - Medications with a **known risk** of prolonging the QT interval within at least 14 days or 5×half-life (whichever is longer) prior to the first dose of study drug (see Appendix 1)
   - Prophylactic use of myeloid growth factors (eg, granulocyte colony-stimulating factor [G-CSF], granulocyte macrophage-colony-stimulating factor [GM-CSF])
6. Major surgery within 14 days of the first dose of study drug; following major surgeries >14 days prior to the first dose of study drug, all surgical wounds must be healed and free of infection or dehiscence
7. Any clinically significant comorbidities, such as significant concomitant arthropathy not related to TGCT in the affected joint, or any other serious medical or psychiatric condition(s), known current alcohol abuse, which in the judgment of the Investigator, could compromise compliance with the protocol, interfere with the interpretation of study results, or predispose the participant to safety risks
8. Active liver or biliary disease including nonalcoholic steatohepatitis (NASH) or cirrhosis
9. Malabsorption syndrome or other illness that could affect oral absorption as judged by the Investigator
10. Known active human immunodeficiency virus (HIV), acute or chronic hepatitis B, acute or chronic hepatitis C, or known active mycobacterium tuberculosis infection
11. If female, the participant is pregnant or breastfeeding
12. Known allergy or hypersensitivity to any component of the study drug

13. Contraindication to MRI

Study Drug, Dosage, and Route of Administration: Vimseltinib 30 mg or matching placebo biw will be administered as oral capsules [redacted]

Reference Therapy, Dosage, and Route of Administration: Not applicable.

Concomitant Medications: All intercurrent medical conditions should be treated by the Investigator according to current community standards of care. Participants may also receive medications for symptomatic relief (eg, analgesics, laxatives, anti-emetics).

Permitted Medications and Therapies but Used with Caution: The following medications should be taken with caution.

- [redacted]
- [redacted]
- [redacted]
- Medications that **may possibly** prolong the QT interval (Appendix 1)

Prohibited Medications and Therapies: The following medications, substances, and procedures are prohibited during study treatment.

- Initiation of any other anti-tumor therapy for TGCT, including radiation or surgery
- Investigational therapy or investigational procedures of any kind
- The use of intra-articular steroid injections for treatment of TGCT; use of intra-articular steroids for a non-TGCT condition is permitted
- Acetaminophen usage exceeding 3 g/day
- Proton-pump inhibitors: discontinue at least 4 days prior to the first dose of study drug
- Medications that are BCRP or OCT2 substrates: discontinue at least 4 days or 5×half-life (whichever is longer) prior to the first dose of study drug
- Medications with a **known risk** of prolonging the QT interval: discontinue at least 14 days or 5×half-life (whichever is longer) prior to the first dose of study drug (Appendix 1)
- Prophylactic use of myeloid growth factors (eg, G-CSF, GM-CSF)

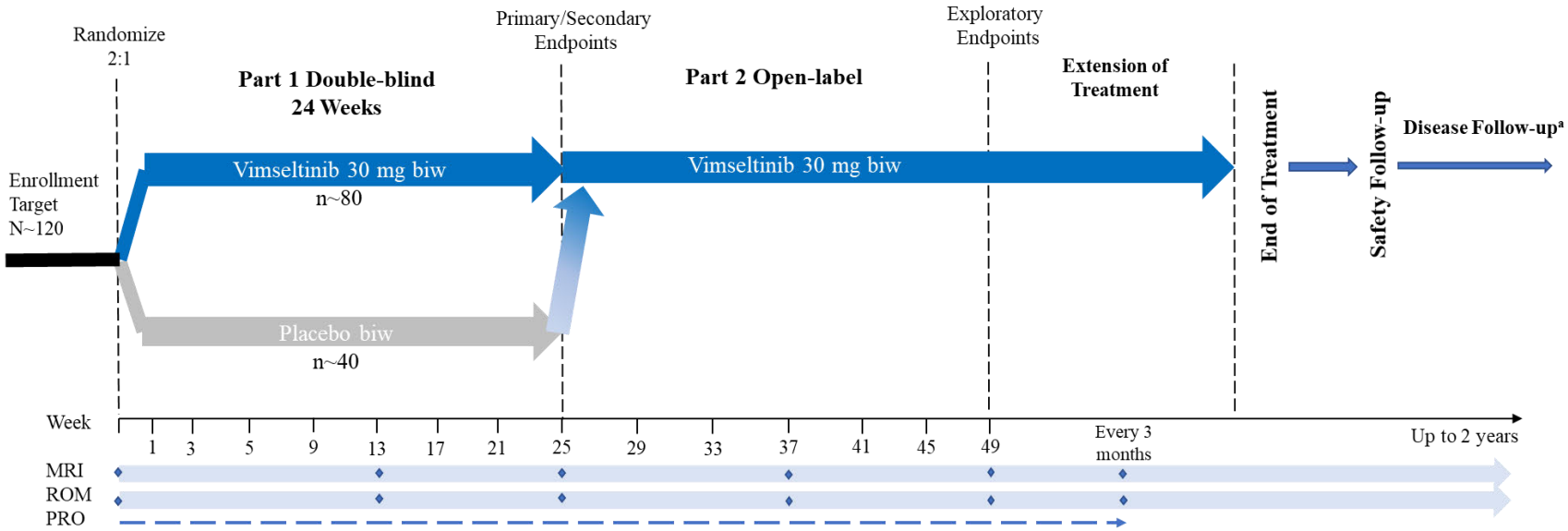
Statistical Methods: Objective response rate will be compared between the 2 treatment arms using a two-sided Cochran-Mantel-Haenszel test stratified by the randomization stratification factors. The test will be performed at a 0.05 alpha level on the intent-to-treat (ITT) set, which includes all randomized participants. A 95% confidence interval (CI) for the proportion in each arm and for the difference in proportion will be presented. Mean change from baseline in ROM, PROMIS-Physical Function score, Worst Stiffness NRS score, and EQ-VAS at Week 25 will be compared between the treatment arms using a mixed model for repeated measurements.

To control overall type I error, a hierarchical testing procedure will be utilized. Statistical testing will be performed for the analysis of primary and key secondary endpoints in the following order at a 2-sided 0.05 alpha level for each:

1. ORR per RECIST v1.1 at Week 25
2. ORR per TVS at Week 25
3. Mean change from baseline in active ROM at Week 25
4. Mean change from baseline in the PROMIS-Physical Function score at Week 25
5. Mean change from baseline in the Worst Stiffness NRS score at Week 25
6. Mean change from baseline in EQ-VAS at Week 25
7. Proportion of responders based on BPI-30 (Worst Pain) NRS score and narcotic analgesic use at Week 25

Sample Size Justification: The study will randomize approximately 120 patients with TGCT in a 2:1 ratio (vimseltinib:placebo) and will have 98% power to detect a statistically significant difference assuming true ORRs of 35% and 5% in the vimseltinib arm and the placebo arm, respectively, using a two-sided Fisher's exact test at 5% level. Sample size selection is based on considerations for powering the analyses of the primary and secondary endpoints.

Figure 1: Study Schema



Patient population:

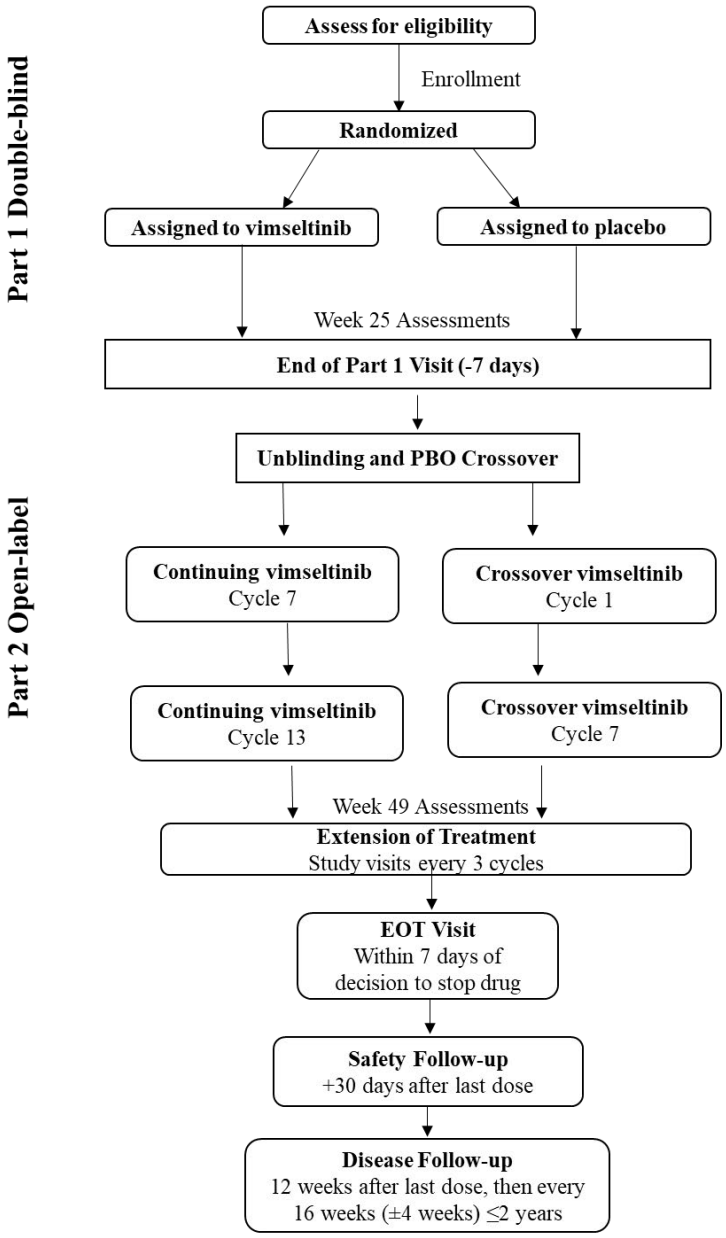
- Histologically confirmed, symptomatic tenosynovial giant cell tumors
- Surgical resection will potentially cause worsening functional limitations or severe morbidity
- No prior use of systemic therapy targeting CSF1 or CSF1R (except imatinib and nilotinib)

Abbreviations: biw=twice weekly; CSF1=colony-stimulating factor 1; CSF1R=colony-stimulating factor 1 receptor; MRI=magnetic resonance imaging; PRO=patient-reported outcome; ROM=range of motion.

[a] Disease follow-up will be performed for up to 2 years.

Note: Participants will be eligible to receive study drug until radiological confirmation of disease progression (refer to Section 10.5), unacceptable toxicity, withdrawal by participant, physician's decision, or commercial availability of vimseltinib and for as long as vimseltinib is being developed to support the indication, and continuation of treatment does not conflict with the Sponsor's right to terminate the study.

Figure 2: Study Visit Flow Schema



Abbreviations: EOT=End-of-Treatment; PBO=placebo.

Table 1: Schedule of Assessments for Part 1 (Double-blind)

Assessments	Screening	Part 1 Double-blind				EOT[a]	Safety Follow-up[b]	Disease Follow-up[c] (up to 2 years after last dose of study drug)	
		C1		C2 to C6	End of Part 1 Visit (Blinded)[d]				
	D-42 to D-1	D1	D15 (±1d)	D1 (±7d)	D1 (±7d)	w/in +7d of decision to stop drug	30 days (±5d) after last dose	12 weeks (±4w) after last dose	Phone contact every 16 weeks (±4w) thereafter
		W1	W3	W5 to W24	W25				
Informed consent	X								
Inclusion/exclusion criteria	X								
Assessment of pain and stiffness symptoms	X								
Demographics/medical history	X								
Confirmation of TGCT diagnosis[e]	X								
Serology testing (hepatitis B/C by central laboratory)	X								
Surgical assessment questionnaire[f]	X					X	X	X	X
Randomization[g]		X							
Pregnancy test[h]	X	X		X	X	X	X		
PE	X				X				
Symptom-directed PE		X	X	X		X	X		
Height (screening only), vital signs and weight[i]	X	X	X	X	X	X	X		
12-lead ECG (local)[j]	X	X	X	X	X	As clinically indicated			
Clinical laboratory tests[k]									

Assessments	Screening	Part 1 Double-blind				EOT[a]	Safety Follow-up[b]	Disease Follow-up[c] (up to 2 years after last dose of study drug)	
		C1		C2 to C6	End of Part 1 Visit (Blinded)[d]				
	D-42 to D-1	D1	D15 (±1d)	D1 (±7d)	D1 (±7d)	w/in +7d of decision to stop drug	30 days (±5d) after last dose	12 weeks (±4w) after last dose	Phone contact every 16 weeks (±4w) thereafter
		W1	W3	W5 to W24	W25				
Hematology (central laboratory)	X	X[k]	X	X	X	X	X		
Serum chemistry (central laboratory)	X	X[k]	X	X	X	X	X		
Coagulation (central laboratory)	X			X	X	X			
Urinalysis (local)	X			X	X	X	X		
Prior/concomitant medications or procedures	30 days prior to first dose through Safety Follow-up								
AE reporting	Continuous from signing informed consent through Safety Follow-up								
Dosing[l]		Oral dosing from C1D1 through C6							
PK sampling[m]		X	X	X[m]		X			
Pharmacodynamic sampling[n]		X	X	X[n]		X[n]			
Tumor tissue[o]	X								
Pharmacogenomics		X (Predose)							
Imaging and response assessment[p]	X[p]			C4 only	X[p]	X[p]		X[p]	
ROM assessment[q]	X			C4 only	X	X[q]			
Investigator questionnaires (CGIC/CGIS)[r]		X	X	X	X	X			

Assessments	Screening	Part 1 Double-blind				EOT[a]	Safety Follow-up[b]	Disease Follow-up[c] (up to 2 years after last dose of study drug)	
		C1		C2 to C6	End of Part 1 Visit (Blinded)[d]				
	D-42 to D-1	D1	D15 (±1d)	D1 (±7d)	D1 (±7d)	w/in +7d of decision to stop drug	30 days (±5d) after last dose	12 weeks (±4w) after last dose	Phone contact every 16 weeks (±4w) thereafter
		W1	W3	W5 to W24	W25				
Patient questionnaires[s]	X		X	X	X	X			
End of Part 1 interview[t]				X					
TGCT therapy/surgery after treatment discontinuation						X	X	X	X
Review of patient dosing diary[u]		Reviewed at every clinic visit through End of Part 1 visit or EOT							
Narcotic analgesic use[v]	Collected during the same 2 consecutive weeks PROs are collected during screening, then C1D1 through End of Part 1 or EOT								
Photographic image of the affected joint[w] (optional)	X	To be performed anytime postbaseline if significant visual change							

Abbreviations: AE=adverse event; C=Cycle; CGIC=clinician global impression of change; CGIS=clinician global impression of severity; D/d=(D)day(s); ECG=electrocardiogram; EOT=End-of-Treatment; MRI=magnetic resonance imaging; PE=physical examination; PF=Physical Function; PK=pharmacokinetics; ROM=range of motion; SAE=serious adverse event; TGCT=tenosynovial giant cell tumor; W=week; w/in=within.

[a] EOT assessments do not need to be repeated if the assessment was done within the previous 7 days.

[b] The Safety Follow-up Visit should be conducted 30 days (±5 days) after the last dose of study drug or prior to the initiation of any new TGCT therapy and/or surgery, whichever comes first. If a participant has been off study drug for more than 30 days at the time of decision to stop treatment, then the Safety Follow-up Visit will be conducted at the EOT visit. Information about new TGCT therapy and/or surgery will be collected during Safety Follow-up.

[c] Disease follow-up will begin 12 weeks (±4 weeks) after last dose of study drug and an MRI will be required at this visit. All subsequent disease follow-up will be conducted by telephone every 16 weeks (±4 weeks) and a review of the participant's medical records for disease status changes will be performed. Disease follow-up will continue for up to 2 years after last dose of study drug, or until disease progression, withdrawal of consent, or start of new TGCT therapy and/or surgery, whichever occurs first. Participants who discontinue study due to confirmed disease progression by IRR will not need to complete Disease Follow-up Visit. Any SAE occurring during this follow-up period must be reported if assessed as related to study drug by the Investigator.

[d] **For conduct of End of Part 1 visit assessments refer to Section 11.5.1. Assessments from End of Part 1 will serve as C1D1 crossover assessments for C1D1 CO (ie, baseline assessments) and C7D1 assessments for participants continuing on study drug in Part 2.** Participants continuing to Part 2 (open label) should follow assessment schedule in Table 2 and Table 3, as applicable, after all required blinded assessments are completed.

[e] Histological confirmation of TGCT diagnosis is required for eligibility. Refer to Section 11.9.2 for more information.

[f] After screening, surgical assessment questionnaire should be completed prior to surgery for participants who proceed to surgery during the study, to capture post-treatment status.

[g] Participants must be randomized within 42 days of screening. After randomization, the first dose of study drug must occur within 3 days of randomization. Participants scheduled for C1D1 on Monday may be randomized on the preceding Friday.

[h] Pregnancy test will be performed by the site for women of childbearing potential. A negative serum pregnancy test is required at screening and a negative serum or urine test is required within 3 days of the first dose at C1D1.

[i] Vital sign measurements will be collected after the participant has been at rest for at least 5 min. Vital signs will include sitting blood pressure, heart rate, respiratory rate, and temperature. Weight will be collected at all study visits. Height will only be obtained at screening.

[j] Single 12-lead ECGs will be obtained after the participant has been at rest for at least 5 min.

[k] Screening labs will be performed within 21 days prior to first dose of study drug. If the screening labs were performed within 3 days before C1D1 then the testing does not need to be repeated on C1D1. For all subsequent visits, a -3 day window is allowed for laboratory assessments. Local laboratory results may be used for treatment management decisions during the study.

[l] Study drug will be administered orally twice weekly at approximately the same time of day beginning on C1D1 CCI [redacted] On all planned PK sampling days, including C1D15, the participant will be dosed in the clinic. On all other visits, participants may dose at home.

[m] Pharmacokinetic sampling will be collected predose (within 60 min before dosing) and 2 hours after dosing (±30 min) on C1D1, C1D15, C2D1, C3D1, then only predose (within 60 min before dosing) on C5D1 or EOT visit, whichever occurs first. On PK sampling days, the order of events should always be ECG, vital signs, and then PK. An unscheduled PK sample may be taken at the time of the onset of a new suspected, treatment-related AE as deemed medically appropriate by the Investigator and Sponsor.

[n] Pharmacodynamic samples (whole blood and plasma) will be collected predose on C1D1, C1D15, C2D1, C3D1, and EOT (if participant does not continue to Part 2). **Asia and Pacific countries only: whole blood sample will not be collected.**

[o] Tumor tissue sample will be collected as available, refer to Section 11.9.17.1.

[p] An MRI of the affected joint will be performed at screening, C4D1 (±7 days of the visit), and End of Part 1 (-7 days of the visit). If a participant discontinues study for reasons other than disease progression or withdrawal of consent in Part 1, an MRI of the affected joint will be performed at End of Part 1 visit, at the EOT visit (if not performed within the previous 30 days), and 12 weeks (±4 weeks) after last dose of study drug at the first Disease Follow-up Visit.

[q] ROM assessment (active and passive) for both the affected joint and non-affected (contralateral) joint will be performed at screening, End of Part 1 visit (-7 days of the visit), and at the EOT (only if not performed within the previous 30 days). At C4D1 (±7 days of the visit), **only the affected joint** will be assessed. Assessments should ideally be performed by the same person for consistency.

[r] CGIS (ROM) and CGIS (PF) will be collected during clinic visits on C1D1, C1D15, D1 of every cycle, at End of Part 1 visit, and at the EOT visit. CGIC, CGIC (ROM), and CGIC (PF) will be collected on C1D15, D1 of every cycle, at End of Part 1 visit, and at the EOT visit.

[s] PRO questionnaires will be delivered on an electronic device per schedule provided in Table 4.

[t] End of Part 1 interviews will be conducted within 28 days before the End of Part 1 (ie, anytime during C6) in the countries where an interviewer is available to conduct in local language. Refer to Section 11.9.15.8 for more information.

[u] Participant will complete a dosing diary daily between site visits. Site staff must review the dosing diary at each clinic visit and collect all completed dosing diaries from the participant.
[v] Narcotic analgesic medication use will be recorded in participant diary (as applicable) during the same 2 consecutive weeks PROs are collected during screening, then C1D1 through End of Part 1 visit or until EOT, whichever occurs first. Site staff must review this diary at each clinic visit and collect all completed narcotic analgesic diaries from the participant.
[w] For additional information, refer to Section 11.9.12.

Table 2: Schedule of Assessments for Part 2 Crossover (Open-label Vimseltinib for Participants Previously Randomized to Placebo in Part 1)

Assessments	C1 CO		C2 CO to C7 CO	C10 CO and every 3 cycles (Extension)	EOT	Safety Follow-up[a]	Disease Follow-up[b] (up to 2 years after last dose of study drug)	
	D1 (±7d)[c]	D15 (±1d)	D1 (±7d)	D1(±7d)	w/in +7d of decision to stop drug	30 days (±5d) after last dose	12 weeks (±4w) after last dose	Phone contact every 16 weeks (±4w) thereafter
	W25	W27	W29 to W49	W61 and every 12 weeks				
Pregnancy test[d]	X		X	X (monthly beginning C8 CO)	X	X		
Symptom-directed PE		X	X	X	X	X		
Vital signs and weight[e]		X	X	X	X	X		
12-lead ECG (local)[f]		X	X	As clinically indicated				
Clinical laboratory tests[g]								
Hematology (central laboratory)		X	X	X	X	X		
Serum chemistry (central laboratory)		X	X	X	X	X		
Coagulation (central laboratory)			X	As clinically indicated	X			
Urinalysis (local)			X	As clinically indicated	X	X		
Concomitant medications/procedures	Continuous through Safety Follow-up							
Surgical assessment questionnaire[h]					X	X	X	X
TGCT therapy/surgery after treatment discontinuation					X	X	X	X
AE reporting	Continuous through Safety Follow-up							
Dosing[i]	Oral dosing to EOT							
PK sampling[j]	X	X	X[j]	X[j]	X			

Assessments	C1 CO		C2 CO to C7 CO	C10 CO and every 3 cycles (Extension)	EOT	Safety Follow-up[a]	Disease Follow-up[b] (up to 2 years after last dose of study drug)	
	D1 (±7d)[c]	D15 (±1d)	D1 (±7d)	D1(±7d)	w/in +7d of decision to stop drug	30 days (±5d) after last dose	12 weeks (±4w) after last dose	Phone contact every 16 weeks (±4w) thereafter
	W25	W27	W29 to W49	W61 and every 12 weeks				
Pharmacodynamic sampling[k]	X	X	X[k]	X[k]	X[k]			
Imaging and response assessment[l]			X	X	X[l]		X	
ROM assessment[m]			X	X	X[m]			
Investigator questionnaires (CGIC/CGIS)[n]		X	X	X	X			
Patient questionnaires[o]		X	X	X	X			
Review of dosing diary[p]	Reviewed at every clinic visit through EOT							
Narcotic analgesic use[q]	Collected through C6 CO or EOT							
Photographic image of the affected joint[r] (optional)	Performed anytime postbaseline if significant visual change							

Abbreviations: AE=adverse event; C=Cycle; CGIC=clinician global impression of change; CGIS=clinician global impression of severity; CO=crossover; D/d=(D)day(s); ECG=electrocardiogram; EOT=End-of-Treatment; MRI=magnetic resonance imaging; PE=physical examination; PF=Physical Function; PK=pharmacokinetics; ROM=range of motion; SAE=serious adverse event; TGCT=tenosynovial giant cell tumor; W=week; w/in=within.

[a] The Safety Follow-up Visit should be conducted 30 days (±5 days) after the last dose of study drug or prior to the initiation of any new TGCT therapy and/or surgery, whichever comes first. If a participant has been off study drug for more than 30 days at the time of decision to stop treatment, then the Safety Follow-up Visit will be conducted at the EOT visit. Information about new TGCT therapy and/or surgery will be collected during Safety Follow-up.

[b] Disease follow-up will begin 12 weeks (±4 weeks) after last dose of study drug and an MRI will be required at this visit. All subsequent disease follow-up will be conducted by telephone every 16 weeks (±4 weeks) and a review of the participant's medical records for disease status changes will be performed. Disease follow-up will continue for up to 2 years after last dose of study drug, or until disease progression, withdrawal of consent, or start of new TGCT therapy and/or surgery, whichever occurs first. Participants who discontinue study due to radiologically confirmed disease progression will not need to complete Disease Follow-up Visit. Any SAE occurring during this follow-up period must be reported if assessed as related to study drug by the Investigator.

[c] End of Part 1 and C1D1 CO both occur on Week 25. Refer to Section 11.5.1 for details.

[d] A local pregnancy test, serum or urine, must be performed within 3 days of first dose of vimseltinib for women of childbearing potential. For subsequent visits, a -3-day window is allowed and can be performed by serum or urine testing. After C7D1 CO (Week 49), serum or urine tests will be performed monthly until

EOT. In between clinic visits, pregnancy testing may be performed at home. If pregnancy testing is performed at home, the Investigator should contact the participant to confirm pregnancy result. Refer to Section 11.9.7 for more information.

[e] Vital sign measurements will be collected after the participant has been at rest for a least 5 min. Vital sign will include sitting blood pressure, heart rate, respiratory rate, and temperature. Weight will be collected at all study visits.

[f] Single 12-lead ECGs will be obtained after the participant has been at rest for a least 5 min. ECGs will be performed only if clinically indicated after C7D1 CO (Week 49).

[g] For all visits, a -3-day window is allowed for laboratory assessments. Local laboratory results may be used for treatment management decisions during the study. Safety samples should be drawn predose at each visit.

[h] Surgical assessment questionnaire should be completed prior to surgery for participants who proceed to surgery during the study, to capture post-treatment status.

[i] Vimseltinib will be administered orally twice weekly at approximately the same time of day beginning on C1D1 CO CCI [redacted] On all planned PK sampling days, including C1D15 CO, the participant will be dosed in the clinic. On all other visits, the participant may take the dose at home.

[j] PK sampling will be collected predose (within 60 min before dosing) and 2 hours after dosing (±30 min) on C1D1 CO, C1D15 CO, C2D1 CO, C3D1 CO, and predose (within 60 min before dosing) on C5D1 CO, C7D1 CO, C10D1 CO, and C13 CO or EOT, whichever occurs first. On PK sampling days, the order of events should be ECG, vital signs, and then PK sample collection. An unscheduled PK sample may be taken at the time of the onset of a new suspected, treatment-related AE as deemed medically appropriate by the Investigator and Sponsor.

[k] Pharmacodynamic samples (whole blood and plasma) will be collected predose on C1D1 CO, C1D15 CO, C2D1 CO, C3D1 CO, C7D1 CO, C10D1 CO, and C13D1 CO or EOT, whichever occur first. **Asia and Pacific countries only: whole blood sample will not be collected.**

[l] An MRI of the affected joint will be performed on, C4D1 CO (±7 days), C7D1 CO (±7 days), Day 1 (±7 days) every 3 cycles thereafter, at the EOT visit (if not performed within the previous 30 days), and 12 weeks (±4 weeks) after last dose of study drug at the first Disease Follow-up Visit. The End of Part 1/C1D1 CO (Week 25) assessment is to be used as baseline for all subsequent imaging assessments.

[m] ROM assessment (active and passive) **of the affected joint only** will be assessed as of C4D1 CO and every 3 cycles (ie, C7D1 CO [±7 days], C10D1 CO [±7 days], etc.), and at the EOT (only if not performed within the previous 30 days). Assessments should ideally be performed by the same person for consistency.

[n] CGIC, CGIC (ROM), CGIC (PF), CGIS (ROM), and CGIS (PF) will be collected during clinic visits through C19D1 CO or EOT, whichever occurs first.

[o] PRO questionnaires will be delivered on an electronic device per schedule provided in Table 5.

[p] Participant will complete a dosing diary daily between site visits. Site Staff must review the dosing diary at each clinic visit and collect all completed dosing diaries from the participant.

[q] Narcotic analgesic medication use will be recorded by participant diary (as applicable) through C6 CO (Week 48) or until EOT, whichever occurs first. Site staff must review this diary at each clinic visit and collect all completed narcotic analgesic diaries from the participant.

[r] For additional information refer to Section 11.9.12.

Table 3: Schedule of Assessments for Part 2 Open-label Vimseltinib (Continuing Treatment for Participants Previously Randomized to Vimseltinib in Part 1)

Assessments	C7	C8 to C12	C13	C16 and every 3 cycles (Extension)	EOT	Safety Follow-up[a]	Disease Follow-up[b] (up to 2 years after last dose of study drug)	
	D1 (±7)[c]	D1 (±7d)	D1 (±7d)	D1 (±7d)	w/in +7d of decision to stop drug	30 days (±5d) after last dose	12 weeks (±4w) after last dose	Phone contact every 16 weeks (±4w) thereafter
	W25	W29 to W45	W49	W61 and every 12 weeks				
Pregnancy test[d]	X	X	X	X (monthly beginning C14)	X	X		
Symptom-directed PE		X	X	X	X	X		
Vital signs and weight[e]		X	X	X	X	X		
12-lead ECG (local)[f]		X	X	As clinically indicated				
Clinical laboratory tests[g]								
Hematology (central laboratory)		X	X	X	X	X		
Serum chemistry (central laboratory)		X	X	X	X	X		
Coagulation (central laboratory)		X	X	As clinically indicated	X			
Urinalysis (local)		X	X	As clinically indicated	X	X		
Concomitant medications/procedures	Continuous through Safety Follow-up							
Surgical assessment questionnaire[h]					X	X	X	X
TGCT therapy/surgery after treatment discontinuation					X	X	X	X
AE reporting	Continuous through Safety Follow-up							
Dosing[i]	Oral dosing to EOT							

Assessments	C7	C8 to C12	C13	C16 and every 3 cycles (Extension)	EOT	Safety Follow-up[a]	Disease Follow-up[b] (up to 2 years after last dose of study drug)	
	D1 (±7)[c]	D1 (±7d)	D1 (±7d)	D1 (±7d)	w/in +7d of decision to stop drug	30 days (±5d) after last dose	12 weeks (±4w) after last dose	Phone contact every 16 weeks (±4w) thereafter
	W25	W29 to W45	W49	W61 and every 12 weeks				
PK sampling[j]	X	X[j]	X		X			
Pharmacodynamic sampling[k]	X	X[k]	X		X[k]			
Imaging and response assessment[l]		X[l]	X	X	X[l]		X	
ROM assessment[m]		X[m]	X	X	X[m]			
Investigator questionnaires (CGIC/CGIS)[n]		X	X	X	X			
Patient questionnaires[o]		X	X[o]	X[o]	X			
Review of dosing diary[p]	Reviewed at every clinic visit through EOT							
Narcotic analgesic use[q]	Collected through C12 or EOT							
Photographic image of the affected joint[r] (optional)	Performed anytime postbaseline if significant visual change							

Abbreviations: AE=adverse event; C=Cycle; CGIC=clinician global impression of change; CGIS=clinician global impression of severity; D/d=(D)day(s); ECG=electrocardiogram; EOT=End-of-Treatment; MRI=magnetic resonance imaging; PE=physical examination; PF=Physical Function; PK=pharmacokinetics; ROM=range of motion; SAE=serious adverse event; TGCT=tenosynovial giant cell tumor; W=week; w/in=within.

[a] The Safety Follow-up Visit should be conducted 30 days (±5 days) after the last dose of study drug or prior to the initiation of any new TGCT therapy and/or surgery, whichever comes first. If a participant has been off study drug for more than 30 days at the time of decision to stop treatment, then the Safety Follow-up Visit will be conducted at the EOT visit. Information about new TGCT therapy and/or surgery will be collected during Safety Follow-up.

[b] Disease follow-up for participants who received vimseltinib treatment will begin 12 weeks (±4 weeks) after last dose of study drug and an MRI will be required at this visit. All subsequent disease follow-up will be conducted by telephone every 16 weeks (±4 weeks) and a review of the participant's medical records for disease status changes will be performed. Disease follow-up will continue for up to 2 years after last dose of study drug, or until disease progression, withdrawal of consent, or start of new TGCT therapy/surgery, whichever occurs first. Participants who discontinue from the study due to radiologically confirmed progression will not need to complete Disease Follow-up Visit. Any SAE occurring during this follow-up period must be reported if assessed as related to study drug by the Investigator.

[c] End of Part 1 and C7D1 both occur on Week 25. Refer to Section 11.5.1 for details.

[d] Pregnancy tests for women of childbearing potential may be performed on or within -3 days of clinic visit by serum or urine testing until Week 49. After C13D1 (Week 49), serum or urine tests will be performed monthly until EOT. In between clinic visits, pregnancy testing may be performed at home. If pregnancy testing is performed at home, the Investigator should contact the participant to confirm pregnancy result. Refer to Section 11.9.7 for more information.

[e] Vital sign measurements will be collected after the participant has been at rest for a least 5 min. Vital signs will include sitting blood pressure, heart rate, respiratory rate, and temperature. Weight will be collected at all study visits.

[f] Single 12-lead ECGs will be obtained locally after the participant has been at rest for a least 5 min. ECGs will be performed only if clinically indicated after C13D1.

[g] For all visits, a -3-day window is allowed for laboratory assessments. Local laboratory results may be used for treatment management decisions during the study. Safety samples should be drawn predose at each visit.

[h] Surgical assessment questionnaire should be completed prior to surgery for participants who proceed to surgery during the study, to capture post-treatment status.

[i] On all planned PK sampling days, the participant will be dosed in the clinic. On all other visits, participants may dose at home.

[j] A single PK sample will be collected predose (within 60 min before dosing) on Day 1 at C7, C10, and C13 (Week 49) or EOT, whichever occurs first. On PK sampling days, the order of events should be ECG, vital signs, and then PK sample collection. An unscheduled PK sample may be taken at the time of the onset of a new suspected, treatment-related AE as deemed medically appropriate by the Investigator and Sponsor.

[k] Pharmacodynamic samples (whole blood and plasma) will be collected predose on C7D1, C10D1, and C13D1 or EOT, whichever occurs first. **Asia and Pacific countries only: whole blood sample will not be collected.**

[l] An MRI of the affected joint will be performed every third cycle after End of Part 1 visit starting on C10D1 (±7 days), Day 1 (±7 days) of every 3 cycles thereafter, at the EOT visit (if not performed within the previous 30 days), and 12 weeks (±4 weeks) after last dose of study drug at the first Disease Follow-up Visit.

[m] ROM assessment (active and passive) **of the affected joint only** will be assessed as of C10D1 and every 3 cycles (ie, C13D1 [±7 days], C16D1 [±7 days], etc.), and at the EOT visit (if not performed within the previous 30 days). Assessments should ideally be performed by the same person for consistency.

[n] CGIC, CGIC (ROM), CGIC (PF), CGIS (ROM), and CGIS (PF) will be collected during clinic visits until C25 or EOT.

[o] PRO questionnaires will be delivered on an electronic device per schedule described in Table 5.

[p] Participant will complete a dosing diary daily between site visits. Site Staff must review the dosing diary at each clinic visit and collect all completed dosing diaries from the participant.

[q] Narcotic analgesic medication use will be recorded by participant diary through C12 (Week 48) or until EOT, whichever occurs first. Site staff must review this diary at each clinic visit and collect all completed narcotic analgesic diaries from the participant.

[r] For additional information refer to Section 11.9.12.

Table 4: Schedule of Patient-reported Outcome Assessments in Part 1

Screening[a]							
Day of Week	**Day 1**	**Day 2**	**Day 3**	**Day 4**	**Day 5**	**Day 6**	**Day 7**
Week 1	BPI NRS	BPI NRS	BPI NRS	BPI NRS	BPI NRS	BPI NRS	BPI NRS PROMIS[b] EQ-5D-5L[b] PGIS (PF)[b] PGIS (ROM)[b]
Week 2	BPI NRS	BPI NRS	BPI NRS	BPI NRS	BPI NRS	BPI NRS	BPI NRS
Cycle 1							
Day of Week	**Day 1**	**Day 2**	**Day 3**	**Day 4**	**Day 5**	**Day 6**	**Day 7**
Week 1		BPI NRS GP5[c]	BPI	BPI NRS	BPI	BPI NRS	BPI
Week 2	BPI NRS	BPI	BPI NRS GP5[c]	BPI	BPI NRS	BPI	
Week 3	BPI NRS GP5[c] PROMIS[c] EQ-5D-5L[c] PGIC[c] PGIS (PF)[c] PGIC (PF)[c] PGIS (ROM)[c] PGIC (ROM)[c]		BPI	BPI NRS	BPI	BPI NRS	BPI
Week 4							

Cycles 2 through 6							
Day of Week	**Day 1**	**Day 2**	**Day 3**	**Day 4**	**Day 5**	**Day 6**	**Day 7**
Week 1	BPI NRS GP5[c] PROMIS[c] EQ-5D-5L[c] PGIC[c] PGIS (PF)[c] PGIC (PF)[c] PGIS (ROM)[c] PGIC (ROM)[c]	BPI	BPI NRS	BPI	BPI NRS	BPI	BPI NRS GP5
Week 2	BPI	BPI NRS	BPI	BPI NRS	BPI	BPI NRS PROMIS[c] GP5[c] PGIS (PF)[c] PGIC (PF)[c]	BPI
Week 3	BPI NRS	BPI	BPI NRS	BPI	BPI NRS GP5[c]	BPI	BPI NRS
Week 4							
End of Part 1							
At End of Part 1 Visit (Blinded, see Table 12**)**	BPI NRS GP5[c] PROMIS[c] EQ-5D-5L[c] PGIC[c] PGIS (PF)[c] PGIC (PF)[c] PGIS (ROM)[c] PGIC (ROM)[c]						

EOT Visit[d]							
Within 7 days of decision to stop drug	BPI NRS GP5 PROMIS EQ-5D-5L PGIC PGIS (PF) PGIC (PF) PGIS (ROM) PGIC (ROM)						

Abbreviations: BPI=Brief Pain Inventory; EOT=End-of-Treatment; EQ-5D-5L=5-level EQ-5D; FACT-G=Functional Assessment of Cancer Therapy-General; GP5="burden-of-side-effects" question from the FACT-G; NRS=numeric rating scale on stiffness; PF=Physical Function; PGIC=patient global impression of change; PGIS=patient global impression of severity; PROMIS=Patient-reported Outcomes Measurement Information System; ROM=range of motion.

[a] Over any 14 consecutive day period during screening, participant must complete at least 4 baseline assessments for BPI (Worst Pain question only) and Worst Stiffness NRS items; and at least one baseline PROMIS assessment, and one baseline EQ-5D-5L assessment to meet entry criteria.

[b] A +7-day window is allowed for completing the PROMIS, PGIS (PF), PGIS (ROM), and EQ-5D-5L questionnaires during screening only.

[c] The GP5, PROMIS, EQ-5D-5L, PGIC, and PGIS questionnaires are allowed a +2-day window during treatment cycles.

[d] No window is allowed at the EOT visit.

Table 5: Schedule of Patient-reported Outcome Assessments in Part 2

Cycles 1 Crossover (crossover participants) or Cycles 7 (participants continuing vimseltinib)							
Day of Week	**Day 1**	**Day 2**	**Day 3**	**Day 4**	**Day 5**	**Day 6**	**Day 7**
Week 1		BPI NRS GP5	BPI	BPI NRS	BPI	BPI NRS	BPI
Week 2	BPI NRS	BPI	BPI NRS GP5	BPI	BPI NRS	BPI	
Week 3	BPI NRS GP5 PROMIS EQ-5D-5L PGIC PGIS (PF) PGIC (PF) PGIS (ROM) PGIC (ROM)		BPI	BPI NRS	BPI	BPI NRS	BPI
Week 4							

Cycles 2 through 6 (crossover participants) **or** **Cycles 8 through 12 (participants continuing vimseltinib)**							
Day of Week	**Day 1**	**Day 2**	**Day 3**	**Day 4**	**Day 5**	**Day 6**	**Day 7**
Week 1	BPI NRS GP5 PROMIS EQ-5D-5L PGIC PGIS (PF) PGIC (PF) PGIS (ROM) PGIC (ROM)	BPI	BPI NRS	BPI	BPI NRS	BPI	BPI NRS GP5
Week 2	BPI	BPI NRS	BPI	BPI NRS	BPI	BPI NRS PROMIS GP5 PGIS (PF) PGIC (PF)	BPI
Week 3	BPI NRS	BPI	BPI NRS	BPI	BPI NRS GP5	BPI	BPI NRS
Week 4							

Cycles 7 through 18 (crossover participants) **or** **Cycles 13 through 24 (participants continuing vimseltinib)**							
Day of Week	**Day 1**	**Day 2**	**Day 3**	**Day 4**	**Day 5**	**Day 6**	**Day 7**
Week 1	BPI NRS GP5 PROMIS EQ-5D-5L PGIC PGIS (PF) PGIC (PF) PGIS (ROM) PGIC (ROM)						
Week 2							
Week 3							
Week 4							
EOT visit							
Within 7 days of decision to stop drug	BPI NRS GP5 PROMIS EQ-5D-5L PGIC PGIS (PF) PGIC (PF) PGIS (ROM) PGIC (ROM)						

Abbreviations: BPI=Brief Pain Inventory; EOT=End-of-Treatment; EQ-5D-5L=5-level EQ-5D; FACT-G=Functional Assessment of Cancer Therapy-General; GP5="burden-of-side-effects" question from the FACT-G; NRS=numeric rating scale on stiffness; PF=Physical Function; PGIC=patient global impression of change; PGIS=patient global impression of severity; PROMIS=Patient-reported Outcomes Measurement Information System; ROM=range of motion.
Note: The GP5, PROMIS, EQ-5D-5L, PGIC and PGIS questionnaires are allowed a +2-day window during treatment cycles until EOT; no window is allowed at the EOT visit.

3. TABLE OF CONTENTS, LIST OF TABLES, AND LIST OF FIGURES

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

4. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

A list of abbreviations and definition of terms is in Table 6.

Table 6: Abbreviations and Definition of Terms

Abbreviation or Specialist Term	Full Form/Definition
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
AST	Aspartate aminotransferase
β-hCG	Beta-human chorionic gonadotropin
BCRP	breast cancer resistance protein
bid	Twice daily
biw	Twice weekly
BPI	Brief Pain Inventory
BPI-SF	Brief Pain Inventory-Short Form
CDC	Centers for Disease Control and Prevention
CGIC	Clinician global impression of change
CGIS	Clinician global impression of severity
CI	Confidence interval
ClinRO	Clinician reported outcome
CO	Crossover
CPK	Creatine phosphokinase
CR	Complete response
CSF1	Colony-stimulating factor 1
CSF1R	Colony-stimulating factor 1 receptor
CTCAE	Common Terminology Criteria for Adverse Events
DLT	Dose-limiting toxicity
DMC	Data monitoring committee
DOR	Duration of response
ECG	Electrocardiogram
eCRF	Electronic case report form
EOT	End-of-Treatment
EQ-5D-5L	5-level EQ-5D

Abbreviation or Specialist Term	Full Form/Definition
EQ-VAS	EuroQol Visual Analogue Scale
FACIT	Functional Assessment of Chronic Illness Therapy
FACT-G	Functional Assessment of Cancer Therapy-General
FDA	U.S. Food and Drug Administration
FSH	Follicle-stimulating hormone
GCP	Good Clinical Practice
G-CSF	Granulocyte colony-stimulating factor
GCT-TS	Giant cell tumor of the tendon sheath
GM-CSF	Granulocyte macrophage-colony-stimulating factor
HIV	Human immunodeficiency virus
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IRR	Independent radiological review
IRT	Interactive response technology
ITT	Intent-to-Treat
LLN	Lower limit of normal
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed model for repeated measurements
mRECIST	Modified RECIST
MRI	Magnetic resonance imaging
NASH	Nonalcoholic steatohepatitis
NCI	National Cancer Institute
NRS	Numeric rating scale
OCT2	Organic cation transporter 2
ORR	Objective response rate
PD	Progressive disease
PF	Physical Function
PGIC	Patient global impression of change
PGIS	Patient global impression of severity

Abbreviation or Specialist Term	Full Form/Definition
CCI	[redacted]
PK	Pharmacokinetic(s)
PP	Per-protocol
PR	Partial response
PRO	Patient-reported outcome
PROMIS	Patient-reported Outcomes Measurement Information System
PROMIS-PF	PROMIS-Physical Function
QoL	Quality of life
QTcF	QT interval corrected by Fridericia's formula
REB	Research Ethics Board
RECIST	Response Evaluation Criteria in Solid Tumors
ROM	Range of motion
RP2D	Recommended Phase 2 dose
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Stable disease
SOD	Sum of Diameters
SUSAR	Suspected unexpected serious adverse reaction
TDS	Tissue damage score
TEAE	Treatment-emergent adverse event
TGCT	Tenosynovial giant cell tumor
TVS	Tumor volume score
ULN	Upper limit of normal
WHO	World Health Organization
WOCBP	Woman of childbearing potential

5. INTRODUCTION

Vimseltinib (DCC-3014) is an oral, small molecule, selective inhibitor of colony-stimulating factor 1 receptor (CSF1R) developed by the Sponsor using its proprietary switch control kinase inhibitor technology platform. CSF1R is a tyrosine kinase receptor expressed predominantly on monocytes and macrophages. Vimseltinib binds to the pocket controlling the conformation of the CSF1R kinase domain and locks the kinase domain in the inactive form. In vitro studies have demonstrated vimseltinib to be a potent and selective inhibitor of CSF1R kinase. Vimseltinib is currently being evaluated for the treatment of advanced solid tumors and tenosynovial giant cell tumor (TGCT) in an ongoing Phase 1/2 clinical development study (Study DCC-3014-01-001; NCT03069469).

5.1. Study Rationale

TGCT is a rare tumor arising from the synovium of joints, bursae, and tendon sheaths. Translocation of the colony-stimulating factor 1 (CSF1) gene has been identified in TGCT patients, resulting in overproduction of CSF1 and recruitment of CSF1R-positive inflammatory cells in the affected joint. While surgery is considered the first treatment option, patients may present with tumors that are considered inoperable or difficult to operate on without subsequent morbidity. In addition, local relapse rates of up to 50% have been reported for diffuse-type TGCT patients, requiring multiple surgeries that can lead to substantial damage to the affected joint and impair quality of life. Vimseltinib is expected to have anti-tumor effects by blocking recruitment of CSF1R-dependent tumor-associated macrophages (TAMs) into the tumor microenvironment. Pexidartinib (Turalio®, 2019), a kinase inhibitor of CSF1R, KIT, and FLT3 was approved by the U.S. Food and Drug Administration (FDA) for systemic treatment of symptomatic TGCT not amenable to improvement with surgery. Pexidartinib is not approved in any other regions and there is currently no approved systemic therapy for symptomatic TGCT outside of the United States. Pexidartinib can cause serious and potentially fatal liver injury and its use requires frequent liver tests for monitoring of liver toxicity. In addition, cognitive impairment may be associated with pexidartinib treatment. Thus, an unmet need remains for a more selective CSF1R inhibitor with an improved safety profile.

5.2. Risk-benefit Assessment

Patients diagnosed with malignant solid tumors or TGCT have enrolled in Phase 1/2 Study DCC-3014-01-001. As of 09 Nov 2021, approximately 54% of patients experienced adverse events (AEs) of Grade 3 or higher. Treatment-emergent AEs of Grade 3 or higher reported in more than 1 TGCT patient were blood creatine phosphokinase (CPK) increased 29 (33.3%), aspartate aminotransferase (AST) increased 4 (4.6%), hypertension 4 (4.6%), lipase increased 3 (3.4%), and amylase increased 3 (3.4%). Observed elevations in transaminase were not associated with symptoms and were not accompanied by bilirubin elevations and/or other signs of liver damage. Safety laboratory values, cardiac function, and clinical signs and symptoms will be monitored throughout the study. Dosing modification guidelines are included in the protocol for AE monitoring (see Section 9.6). Please refer to the Investigator's Brochure (IB) for currently available clinical safety data.

Effects on embryo-fetal development were studied in rats, and vimseltinib was determined CCI [redacted] Participants in this study are advised to avoid pregnancy and are

required to use highly effective contraception during the study and for 60 days following the last dose of study treatment for females and 120 days for males. Additional details on the available nonclinical toxicology data and clinical safety data are provided in the IB.

Among efficacy evaluable TGCT patients, objective responses were observed as measured by Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 by independent radiological review (IRR) that were sustainable over time. Updated anti-tumor activity data as of 07 Jun 2021 demonstrated an objective response rate (ORR) of 50% in 32 patients across 3 dose escalation cohorts, and an ORR of 42% (all partial response [PR]) in 19 patients in expansion Cohort A at the recommended Phase 2 dose (RP2D), which is also the selected Phase 3 dose. Objective responses were generally achieved after at least 2 cycles of treatment and responses were durable.

The clinical experience continues to support further study of vimseltinib in the TGCT patient population. The risk to participants appears acceptable, and the benefit-risk balance of vimseltinib treatment in TGCT patients for the Phase 3 study is considered positive.

6. STUDY OBJECTIVES AND ENDPOINTS

6.1. Objectives

Primary Objective:

- To evaluate anti-tumor activity of vimseltinib using RECIST v1.1 by blinded IRR

Secondary Objectives:

- To assess anti-tumor activity of vimseltinib using tumor volume score (TVS) and modified RECIST (mRECIST) by blinded IRR
- To assess the effects of vimseltinib on range of motion (ROM)
- To assess the effects of vimseltinib on physical function, worst stiffness, worst pain, and quality of life (QoL) using patient-reported outcome (PRO) measures
- To assess safety and tolerability of vimseltinib

Exploratory Objectives:

- To assess the correlation of pharmacokinetics (PK) with efficacy and/or safety
- To assess the pharmacodynamic effects of vimseltinib in relation to safety or efficacy
- To assess germline polymorphic variations in genes involved in the metabolism or disposition of vimseltinib or in relation to safety or efficacy
- To assess long-term safety and efficacy of vimseltinib
- To assess the effects of vimseltinib on symptomatic relief and functional assessments

6.2. Endpoints

Primary Endpoint:

- Objective response rate (ORR, including complete response [CR] and PR) per RECIST v1.1 at Week 25

Key Secondary Endpoints:

- ORR per TVS at Week 25
- Change from baseline in active ROM of the affected joint, relative to a reference standard, at Week 25
- Change from baseline in the Patient-reported Outcomes Measurement Information System (PROMIS) physical function score at Week 25
- Change from baseline in the Worst Stiffness numeric rating scale (NRS) score at Week 25
- Change from baseline in EQ-VAS (EuroQol Visual Analogue Scale) at Week 25

- Response of at least a 30% improvement in the mean Brief Pain Inventory (BPI) Worst Pain NRS score without a 30% or greater increase in narcotic analgesic use at Week 25

Other Secondary Endpoints:

- ORR per RECIST v1.1
- ORR assessed by mRECIST at Week 25
- Duration of response (DOR; time from first PR or CR to disease progression or death) assessed using RECIST v1.1, TVS, and mRECIST
- Incidence of treatment-emergent adverse events (TEAEs), treatment-emergent serious adverse events, related TEAEs, dose reductions, dose interruptions, and discontinuation of study drug due to adverse event
- Changes from baseline in laboratory parameters, electrocardiograms (ECGs), and vital signs

Exploratory Endpoints:

Pharmacokinetics

- Correlation of PK with efficacy and/or safety

Pharmacodynamics

- Effects of pharmacodynamics in relation to safety or efficacy

Pharmacogenomics

- Germline polymorphisms in genes involved in the metabolism or disposition of vimseltinib or related to safety and/or efficacy

Efficacy and functional assessments

- ORR at Week 49
- Change from baseline in tissue damage score (TDS)
- Change from baseline in active ROM of the affected joint, relative to a reference standard, at Week 49
- Change from baseline in active ROM of the affected joint, relative to the contralateral joint, at Week 25
- Change from baseline in passive ROM of the affected joint, relative to a reference standard, at Week 25
- Change from baseline in passive ROM of the affected joint, relative to a contralateral joint, at Week 25
- Clinician Reported Outcome (ClinRO) and PRO assessments at Week 13 and Week 49
- Additional ClinRO and PRO assessments:

- Response of at least a 30% improvement in the mean BPI Average Pain NRS score without a 30% or greater increase in narcotic analgesic use at Week 25
- Patient global impression of change (PGIC) and clinician global impression of change (CGIC) up to Week 25
- Patient global impression of severity (PGIS) and clinician global impression of severity (CGIS) up to Week 25
- GP5 “burden-of-side-effects” question from the Functional Assessment of Cancer Therapy-General (FACT-G) at Week 25: response of 3 (“quite a bit”) or 4 (“very much”)

7. INVESTIGATIONAL PLAN

7.1. Overall Study Design

This is a multicenter, randomized, placebo-controlled study of vimseltinib in patients with TGCT, consisting of 2 parts: Part 1 is double-blinded and Part 2 is open label. Symptomatic patients with histologically confirmed TGCT for whom surgical resection will potentially cause worsening functional limitation or severe morbidity will be eligible. Patients who received anti-CSF1/CSF1R therapy previously (except for imatinib or nilotinib) will be excluded. The study will evaluate efficacy, safety, clinical outcome assessments, PK, and pharmacodynamics of vimseltinib in this population.

The study will consist of a 42-day screening period prior to the first dose of study drug, a Part 1 double-blinded treatment period of 24 weeks (referred to in 28-day cycles) and a Part 2 open-label period until Week 49 (Figure 1). Participants will continue treatment after Week 49 during the extension period. There will also be an End-of-Treatment (EOT) Visit within 7 days after the decision to stop study drug, a Safety Follow-up Visit 30 days (±5 days) after the last dose of study drug, and a Disease Follow-up period of up to 2 years or until initiation of new TGCT treatment or surgery, whichever occurs first. A summary of visit flow is provided in Figure 2. Participants will be allowed to undergo surgical resection only after completion of Part 1.

Approximately 120 participants will be randomized in a 2:1 ratio to receive either vimseltinib at the dose of 30 mg twice weekly (biw) (n=80) or placebo (n=40) for 24 weeks. Randomization will be stratified for tumor location (lower limb/all other) and region (U.S./non-U.S.).

At Week 25, the primary and secondary endpoints will be assessed, and participants randomized to placebo in Part 1 will have the option to crossover and receive open-label vimseltinib in Part 2 upon completion of Part 1. Participants randomized to placebo in Part 1 with confirmed disease progression by blinded IRR before Week 25 are eligible for early entry into Part 2. Participants randomized to vimseltinib in Part 1 with confirmed disease progression by IRR before Week 25 will discontinue from study, while those without confirmed disease progression by IRR before Week 25 will continue to receive vimseltinib in Part 2 upon completion of Part 1.

Anti-tumor activity will be assessed by RECIST v1.1. Tumor volume score and mRECIST will be used as additional assessments of anti-tumor activity. Range of motion assessments will be performed and PRO measures will be collected. Safety will be assessed using Common Terminology Criteria for Adverse Events (CTCAE) v5.0. Correlation between efficacy or safety with PK and pharmacodynamics will be explored.

7.2. Rationale for Study Design

The double-blind and randomized design of this study will allow for adequate assessment of vimseltinib compared to a control group. The selection of placebo as the control group is justified because in most participating countries there are no approved systemic, nonsurgical therapies for the treatment of TGCT in patients not amenable to surgery. While pexidartinib is approved in the United States, it is associated with a risk of potentially fatal liver injury and available under restricted access (REMS program) (Turalio, 2019). It is anticipated that patients

in the United States, after being counseled on their treatment options, may choose to forego pexidartinib due to its undesirable safety profile, hair color changes, or accessibility issues.

Further, TGCT is a non-life-threatening and slowly progressing disease. Based on the clinical outcome assessment data from TGCT patients randomized to the placebo arm of the ENLIVEN study, rapid symptomatic progression is not expected during the 24-week time course on placebo. Patients with this condition typically do not deteriorate rapidly and, despite symptom burden, may choose to enroll in a placebo-controlled study that includes a provision for crossover following a limited treatment course (24 weeks) for participants randomized to placebo. Participants randomized to either placebo or vimseltinib will receive supportive standard of care during the study. The 2:1 randomized design will minimize the number of participants on placebo. Additionally, the protocol allows for participants to crossover to open-label vimseltinib in the event of disease progression (confirmed by IRR) earlier than 24 weeks, and all participants may choose to remain on study to receive open-label vimseltinib in Part 2.

7.3. Justification for Dose

CCI [redacted].

CCI [redacted]

CCI [redacted]

Based on an acceptable and manageable safety profile and the objective responses observed in Cohort 5, 30 mg biw without a loading dose was selected as the RP2D for TGCT patients to further evaluate safety and efficacy in Phase 2 expansion cohorts and this Phase 3 study. The loading dose was not recommended as it was not considered necessary in patients with a nonmalignant, non-life-threatening disease such as TGCT.

The available clinical data provided in the current IB and in Section 5.2 continue to support the selected dose for this Phase 3 study.

7.4. Duration of Treatment

Participants will be eligible to receive study drug until radiological confirmation of disease progression (refer to Section 10.5), unacceptable toxicity, withdrawal by participant, physician's decision, or commercial availability of vimseltinib, and for as long as vimseltinib is being developed to support the indication, and continuation of treatment does not conflict with the Sponsor's right to terminate the study.

7.5. End of Study Definition

The end of the study is defined as the date of the last visit of the last participant in the study or last scheduled procedure shown in schedule of assessments for the last participant in the study.

8. STUDY POPULATION

8.1. Inclusion Criteria

Participants must meet all of the following criteria to be eligible to enroll in the study:

1. Male or female participants ≥18 years of age
2. Histologically confirmed diagnosis of TGCT (formerly known as pigmented villonodular synovitis [PVNS] or giant cell tumor of the tendon sheath [GCT-TS]). Tumor biopsy to confirm TGCT diagnosis will be required if no histology/pathology is available
    a. Participants should have TGCT in a single joint and must have TGCT in joints where ROM can be assessed
3. Disease for which surgical resection will potentially cause worsening functional limitation or severe morbidity as judged by surgical consultation or a multidisciplinary tumor board
4. Symptomatic disease with at least moderate pain or at least moderate stiffness (defined as a score of 4 or more, with 10 describing the worst condition) within the screening period and documented in the medical record
5. Participant should complete 14 consecutive days of questionnaires during the screening period and must meet minimum requirements as outlined in Table 4
6. An analgesic regimen, if used, needs to be stable (ie, no change in dose) as judged by the Investigator for at least 2 weeks prior to the first dose of study drug
7. Measurable disease per RECIST v1.1 with at least one lesion having a minimum size of 2 cm, as assessed from magnetic resonance imaging (MRI) scans by a central radiologist
8. Adequate organ function and bone marrow reserve as indicated by the following laboratory assessments performed within 21 days prior to the first dose of study drug:
    a. Bone marrow function: absolute neutrophil count (ANC) ≥1500/µL; hemoglobin ≥10 g/dL; platelet count ≥lower limit of normal (LLN)
    b. Hepatic function: total serum bilirubin ≤upper limit of normal (ULN); serum AST/ALT ≤ULN
    c. Renal function: creatinine clearance ≥50 mL/min based either on urine collection or Cockcroft-Gault estimation
    d. Electrolytes ≥LLN for: potassium, magnesium, and calcium
9. Able to take oral medication
10. Participants of reproductive potential must:
    a. Have a negative serum beta-human chorionic gonadotropin (β-hCG) pregnancy test at screening (female participants)
    b. Agree to follow the contraception requirements outlined in the protocol
11. The participant is capable of understanding and complying with the protocol and has signed the informed consent form (ICF). A signed ICF must be obtained before any study-specific procedures are performed

12. Willing and able to complete the PRO assessments on an electronic device

8.2. Exclusion Criteria

Participants meeting any of the following criteria will be excluded from the study:

1. Previous use of systemic therapy (investigational or approved) targeting CSF1 or CSF1R including vimseltinib; previous therapy with imatinib and nilotinib is allowed
2. Treatment for TGCT, including investigational therapy, during the screening period

   NOTE: Participants may not be part of an ongoing or have prior participation in a non-TGCT investigational drug study within 30 days of screening. Ongoing participation in a noninterventional study (including observational studies) is permitted.
3. Known metastatic TGCT or other active cancer that requires concurrent treatment (exceptions will be considered on a case-by-case basis depending on tumor type, stage, location, planned treatment, and expected recovery after discussion and approval by Sponsor)
4. Baseline prolongation of the QT interval corrected by Fridericia's formula (QTcF) based on repeated demonstration of QTcF >450 ms in males or >470 ms in females or history of long QT syndrome
5. Receive concurrent treatment with any prohibited medications
   - Acetaminophen usage exceeding 3 g/day
   - Proton-pump inhibitors taken within 4 days prior to the first dose of study drug
   - Medications that are breast cancer resistance protein (BCRP) or organic cation transporter 2 (OCT2) substrates taken within at least 4 days or 5×half-life (whichever is longer) prior to the first dose of study drug
   - Medications with a known risk of prolonging the QT interval within at least 14 days or 5×half-life (whichever is longer) prior to the first dose of study drug (see Appendix 1)
   - Prophylactic use of myeloid growth factors (eg, granulocyte colony-stimulating factor [G-CSF], granulocyte macrophage-colony-stimulating factor [GM-CSF])
6. Major surgery within 14 days of the first dose of study drug; following major surgeries >14 days prior to the first dose of study drug, all surgical wounds must be healed and free of infection or dehiscence
7. Any clinically significant comorbidities, such as significant concomitant arthropathy not related to TGCT in the affected joint, or any other serious medical or psychiatric condition(s), known current alcohol abuse, which in the judgment of the Investigator, could compromise compliance with the protocol, interfere with the interpretation of study results, or predispose the participant to safety risks
8. Active liver or biliary disease including nonalcoholic steatohepatitis (NASH) or cirrhosis
9. Malabsorption syndrome or other illness that could affect oral absorption as judged by the Investigator

10. Known active human immunodeficiency virus (HIV), acute or chronic hepatitis B, acute or chronic hepatitis C, or known active mycobacterium tuberculosis infection
11. If female, the participant is pregnant or breastfeeding
12. Known allergy or hypersensitivity to any component of the study drug
13. Contraindication to MRI

8.3. Restrictions/Cautions

- To mitigate the potential risk of photo irritation/phototoxicity, participants will be instructed to avoid strong sunlight, sunlamps, and other sources of ultraviolet radiation for the duration of the study.
- Prophylactic skin care recommendations for all participants on study drug include sunscreen with sun protection factor ≥30, hypoallergenic moisturizing creams or ointments for dry skin, and gentle skincare with fragrance-free soaps and detergents as described in Section 9.6.3.3.

8.4. Contraceptive Requirements

8.4.1. Definition of Woman of Childbearing Potential

Women in the following categories are not considered women of childbearing potential (WOCBP):

- Postmenopausal: spontaneous amenorrhea for ≥12 consecutive months and/or have a serum follicle-stimulating hormone (FSH) level ≥40 mIU/mL
- Documented hysterectomy or a bilateral oophorectomy/salpingo-oophorectomy

All other female participants (including those with tubal ligations) will be considered to be of childbearing potential.

8.4.2. Contraceptive Use

CCI [redacted] Women should be advised to avoid pregnancy while taking vimseltinib. CCI [redacted] Participation in this study requires participants receiving vimseltinib to agree to use 2 methods of contraception with one of the methods being highly effective. Methods of contraception must be in successful use from at least 14 days prior to the first dose of vimseltinib and until 60 days following the last dose of study drug for female participants and 120 days for male participants. If hormonal contraception is used, then it should be in successful use for at least 7 days prior to first dose.

Contraception for the participant is waived for the following:

- True abstinence for the participant, when this is in line with the preferred and usual lifestyle of the participant. Periodic abstinence (eg, calendar, ovulation, symptothermal, and postovulation methods) and withdrawal are not acceptable methods of contraception.

- If the male has documented bilateral orchiectomy or is considered infertile as documented through examination of a semen specimen or by demonstration of the absence of the vas deferens by ultrasound before the first dose of the study drug.
- If the female is of nonchildbearing potential, per Section 8.4.1

Acceptable highly effective methods of contraception:

- Vasectomy 6 months or more previously, with a negative postvasectomy semen analysis for sperm
- Bilateral tubal ligation performed at least 6 months previously
- Continuous use of an intrauterine device for at least 90 days prior to the first dose of the study drug
- Combined (estrogen and progestin containing) or progestin-only hormonal contraception associated with inhibition of ovulation:
  - oral
  - intravaginal
  - transdermal
  - injectable
  - implantable

Acceptable methods of contraception:

- Male or female condom with or without spermicide
- Barrier contraception (such as diaphragm, cervical cap, or sponge) and spermicide
  - In countries where spermicide is not available, barrier contraception without spermicide is acceptable

Additional notes: Acceptable methods of contraception listed above are examples. Local requirements may prohibit the use of some of these examples. Please contact the Sponsor with any questions.

- Female condom cannot be used with male condom (as a double method of contraception) due to risk of tearing
- Male and female participants who are not sexually active at the time of screening must agree to follow the contraceptive requirements of this study before they become sexually active with a partner of the opposite sex
- If applicable, additional contraception requirements may need to be followed according to local regulations and/or requirements
- Male participants must not donate sperm after the first dose of study drug, throughout the study, and for 120 days following the last dose of study drug

- Female participants must not plan to become pregnant during the study through 60 days following the last dose of study drug and 120 days for female partners of male participants
- Male participants whose female partner becomes pregnant through well-documented in vitro fertilization (donated sperm) or banked sperm (collected before the participant received study drug) must be compliant with the contraception requirements. In this scenario, the male participant must commit to using acceptable methods of contraception (to ensure there is no exposure of the fetus to study drug) for the duration of the study and until 120 days after the last dose of study drug

Unique situations that may not fall within the above specifications must be discussed with the Sponsor.

If there is any question that a female of childbearing potential or male participant will not reliably comply with the requirements for contraception, that participant must not be entered into the study.

8.5. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently assigned to a treatment arm. Information on participants who screen fail is recorded in the Interactive Response Technology (IRT).

8.6. Rescreening

Participants may be rescreened once with Sponsor's approval. Rescreened participants will retain their original participant number and all screening assessments will be repeated in Table 1 except for MRI scan. MRI scan will only be repeated if performed >42 days before first dose of study drug. If a participant is rescreened, the screening window will begin once the first rescreening assessment has been initiated.

9. STUDY DRUG MATERIALS AND MANAGEMENT

9.1. Study Drug

Information regarding study drug are summarized in Table 7. In this protocol, study drug will refer to vimseltinib and placebo.

Vimseltinib (DCC-3014) will be provided as 2 mg and 10 mg capsules for oral administration.

Placebo will be supplied as identically sized and color-matched capsules.

Table 7: Study Drugs

Study Arm	Vimseltinib	Placebo
Intervention Name	Vimseltinib	Placebo
Dose Formulation	Capsule	Capsule
Unit Dose Strengths	2 mg, 10 mg	Matching placebo
Dosage Level	30 mg biw	Same frequency as vimseltinib
Route of Administration	Oral	Oral
Physical Description	Size 4, hard gelatin capsules: 2 mg (blue) and 10 mg (white)	Identically sized and color-matched capsules
Use	Experimental	Placebo comparator
IMP/NIMP	IMP	IMP
Sourcing	Provided centrally by the Sponsor	Provided centrally by the Sponsor
Packaging and Labeling	Vimseltinib will be provided in 30-count high density polyethylene bottles with an induction seal/child-resistant closure. Each bottle will be labeled as required per country regulations.	Identically packaged as active drug. Each bottle will be labeled as required per country regulations.

Abbreviations: biw=twice weekly; IMP=investigational medicinal product; NIMP=non-investigational medical product.

9.2. Study Drug Storage

Vimseltinib and placebo bottles must be stored in a secure, temperature-monitored location with limited access and according to the labeled storage conditions. Temperature monitoring is required at the clinical site throughout the duration of the study. Detailed instructions for storage and handling of the study drug at the clinical site and after dispensation to participants will be provided in the Pharmacy Manual.

9.3. Study Drug Preparation

Not applicable.

9.4. Methods of Assigning Participants to Treatment

Participants will be randomized in a 2:1 ratio to receive either vimseltinib 30 mg biw or placebo in the double-blind portion of the study (Part 1). Randomization will be stratified by:

- Tumor location: lower limb or all other
- Region: U.S. or non-U.S.

Interactive Response Technology will be used to randomize and assign study drug. Detailed instructions to randomize and assign treatment will be provided separately in the IRT Site User Manual.

9.4.1. Blinding

In Part 1 of the study, the participants and all site personnel, including the Investigator, the site monitor, and the study team must be blinded to study drug treatment, with the exception of the following:

- Any site personnel for whom this information is important to ensure the safety of the participant in the event of a life-threatening medical emergency
- Any site personnel for whom this information is important to ensure the safety of the participant and their fetus in the event of a pregnancy
- Vendors responsible for pharmacovigilance and regulatory personnel at the Sponsor to satisfy serious adverse event (SAE) processing and reporting regulations
- Clinical supply chain personnel at the Sponsor and the vendor
- Unblinded statistician and programmer preparing the final (production) randomization list and unblinded analyses for the data monitoring committee (DMC)
- DMC
- Vendors analyzing PK and biomarker samples
- Vendor conducting the population PK analysis
- IRT vendor
- The Investigator, participant, site personnel, site monitor and study team will become unblinded to a specific participant's treatment assignment, if the participant has disease progression based on IRR or have reached Week 25 and completed End of Part 1 assessments.

9.4.2. Unblinding During Part 1

In exceptional circumstances, emergency unblinding is possible during Part 1 if, in the Investigator's opinion, immediate unblinding of the treatment is necessary for further management of the participant. Participants who are unblinded for emergency will be permanently discontinued from the study.

The Investigator is encouraged to contact the Sponsor or designee and discuss the participant's situation before making the decision to unblind.

Additionally, participants with disease progression confirmed by IRR before completion of Part 1 (ie, Week 25) will be unblinded. Additional information is provided in Section 10.5.

9.4.3. Unblinding at End of Part 1 Visit

After completion of the End of Part 1 assessments, participants who wish to continue to the open-label part of this study (Part 2) will be unblinded. Participants randomized to placebo will crossover to receive vimseltinib and participants initially randomized to vimseltinib will continue to receive vimseltinib in Part 2.

9.5. Study Drug Administration

During Part 1, vimseltinib or matching placebo capsules should be administered orally on Day 1 and Day 5 each week at approximately the same time of day. CCI [redacted] Each dose may be taken within 24 hours of the scheduled dosing time (±1 day window). There should always be at least 24 hours between doses. If the participant missed the scheduled dose, then that dose should be skipped. The next required dose should be taken at the next scheduled time and the participant should not double the dose to make up for an earlier missed dose. Should a participant vomit after dosing, the study drug will not be re-administered.

CCI [redacted]

After unblinding, participants randomized to vimseltinib in Part 1 and continuing to Part 2 should be instructed to take the same number of capsules per day as they were taking at the End of Part 1 (ie, they will remain at reduced dose if the dose was reduced). Participants randomized to placebo in Part 1 and who choose to continue to Part 2 will initiate vimseltinib 30 mg biw on Crossover Cycle 1 Day 1.

Participants may receive the COVID-19 vaccine or booster while receiving study drug. Participant should schedule the vaccination on the day when dosing with the study drug is not expected. If not possible, the participant should take the study drug at least 2 hours before or after receiving the vaccination or booster.

If a participant receives the COVID-19 vaccination or booster during screening, it is recommended to start study drug at least 7 days after the day of vaccination.

If required, study drug may be shipped directly to a participant if they are not able to attend a study visit following the instructions detailed in the Pharmacy Manual.

9.6. Criteria for Dose Interruption and Modification

Study drug may be interrupted and/or modified at the discretion of the Investigator at any time due to AEs. Study drug may also be interrupted for other reasons in consultation with the Sponsor Medical Monitor. Any study drug interruption unrelated to an AE will be limited to 28 days. Upon resumption of study drug following a dose interruption, the Investigator must continue with the participant's original visit schedule calculated from Cycle 1 Day 1. Clinic visits and assessments should continue during dose interruptions.

9.6.1. Dose Interruption and Modification

CCI

[redacted]

9.6.2. Dose Reduction Steps for Study Drug

If dose reduction is required, dose reduction steps are as described in Table 8.

Table 8: Dose Reduction Steps for Study Drug

Dose of Study Drug at the Time of Dose Modification	Dose Reduction
30 mg	20 mg
20 mg	14 mg

If a dose reduction of study drug is required, re-escalation of dose may be permitted based on agreement between the Investigator and Sponsor.

A participant will be allowed to have 2 dose level reductions. If more than 2 dose level reductions are required, the study drug will be discontinued.

9.6.3. Dose Interruption and Management of Toxicities

9.6.3.1. Guidelines for Hepatobiliary Lab Elevations

Recommended dose interruption and management of treatment-related hepatobiliary lab elevations are shown in Table 9.

Table 9: Dose Interruption and Management of Treatment-related Hepatobiliary Laboratory Elevations

Toxicity Grade CTCAE v5.0	Dose Interruption and Management
Grade 2 ALT and/or AST increase **(>3–5×ULN)** and total bilirubin ≤ULN	Continue treatment with study drug Check for changes to medications and symptoms Perform confirmation liver enzyme (AST, ALT and ALP) and bilirubin tests within 48-72 hours Repeat liver enzyme tests weekly for 8 weeks to ensure stability
Grade 2 ALT and/or AST increase **(>3–5×ULN)** and total bilirubin increase **up to 2×ULN** **OR** Total bilirubin increase **up to 2×ULN**	Hold treatment with study drug Check for changes to medications and symptoms Perform confirmation liver enzyme (AST, ALT, and ALP) and bilirubin tests within 48-72 hours Repeat liver enzyme tests weekly Study drug may be resumed at 1 dose level reduction once Hy's law has been definitively ruled out, labs resolve to Grade 1 or baseline, after discussion with Sponsor **If ALT/AST/bilirubin continue to increase,** or the increased level persists more than 28 days: • Discontinue study drug • Refer for gastroenterology/hepatology consultation • Consider liver ultrasound

Toxicity Grade CTCAE v5.0	**Dose Interruption and Management**
Grade 2 ALT and/or AST increase **(>3–5×ULN)** and total bilirubin increase **>2×ULN** or INR >1.5 **and** ALP **<2×ULN** **OR** Total bilirubin increase **>2×ULN**	Hold treatment with study drug Check for changes to medications and symptoms Perform confirmation liver enzyme (AST, ALT and ALP), bilirubin, and INR tests within 48-72 hours Refer for gastroenterology/hepatology consultation Consider liver ultrasound Repeat liver enzyme, bilirubin, and INR tests weekly until resolution to Grade 1 or baseline Study drug may be resumed at 1 dose level reduction once Hy's law has been definitively ruled out, labs resolve to Grade 1 or baseline, after discussion with Sponsor **If ALT/AST/bilirubin/INR continue to increase**, or the increased level persists more than 28 days: • Discontinue study drug
Grade 3 ALT and/or AST increase **(>5–8×ULN)** and total bilirubin **≤ULN and without clinical symptoms**	Hold treatment with study drug Check for changes to medications and symptoms Perform confirmation liver enzyme (AST, ALT and ALP) and bilirubin tests within 48-72 hours Repeat liver enzyme tests weekly until resolution to Grade 1 or baseline Study drug may be resumed at 1 dose level reduction once labs resolve to Grade 1 or baseline, after discussion with Sponsor **If ALT/AST/bilirubin continue to increase,** or the increased level persists more than 28 days: • Discontinue study drug • Refer for gastroenterology/hepatology consultation • Perform liver ultrasound
Grade 3 ALT and/or AST increase **(>5-8×ULN)** and total bilirubin increase **>ULN** or INR >1.5 or ALP **>2×ULN**	Discontinue treatment with study drug Check for changes to medications and symptoms Perform confirmation liver enzyme (AST, ALT, and ALP), bilirubin, and INR tests within 48-72 hours Consider gastroenterology/hepatology consultation Perform liver ultrasound Repeat liver enzyme, bilirubin, and INR tests at least twice weekly until resolution to Grade 1 or baseline
Grade ≥3 ALT and/or AST increase **(>8×ULN)**	Discontinue treatment with study drug Check for changes to medications and symptoms Repeat liver enzymes and bilirubin tests at least twice weekly until resolution to Grade ≤2

Toxicity Grade CTCAE v5.0	Dose Interruption and Management
	Refer for gastroenterology/hepatology consultation Perform liver ultrasound

Abbreviations: ALP=alkaline phosphatase; ALT=alanine aminotransferase; AST=aspartate aminotransferase; CTCAE=Common Terminology Criteria for Adverse Events; INR=international normalized ratio; ULN=upper limit of normal.
Note: Cases of Hy's law must be reported as a serious adverse event and study drug must be discontinued immediately.

9.6.3.2. Guidelines for Prolonged QTcF Interval

Recommended dose interruption and management of treatment-related prolonged QTcF interval is provided in Table 10.

Table 10: Recommended Dose Interruption and Management of Treatment-related Prolonged QTcF Interval

Toxicity Grade CTCAE v5.0 (ECG QTc interval prolonged)	Dose Interruption and Management
Grade 2 (QTc 481-500 ms)	• Continue study drug • Continue ECG monitoring per protocol
Grade 3 (QTc ≥501 ms; >60 ms change from baseline)	• Hold treatment with study drug • Continue close ECG monitoring and consult cardiologist • Upon resolution to Grade 1 or baseline in ≤14 days, may resume study treatment at same dose. If >14 days for resolution to Grade 1 or baseline, may resume study treatment at reduced dose.
Grade 4	• Discontinue study drug • Continue close ECG monitoring and consult cardiologist

Abbreviations: CTCAE=Common Terminology Criteria for Adverse Events; ECG=electrocardiogram; QTc=QT interval corrected; QTcF=QT interval corrected by Fridericia's formula.

9.6.3.3. Guidelines for Dermatologic Adverse Events

Recommended dose interruption and management of treatment-related skin and subcutaneous disorder and recommendations for management of dry skin are presented in Table 11.

General guidelines for treatment-related dermatologic adverse events:

- Symptoms and signs of hypersensitivity reaction should be monitored at each clinic visit. Refer to Section 9.6.1 for dose interruption guidance
- Use "Rule of 9s" (refer to Appendix 2) to calculate body surface area (BSA) for CTCAE grading

- Participant should be advised to use fragrance-free detergents and soaps, wear sunscreen with sun protection factor ≥30, and moisturize the skin at least once daily, preferably twice daily
- Standardized photos for any Grade ≥2 dermatologic AEs should be submitted to the Sponsor
- A skin biopsy sample (ie, punch biopsy) may be collected locally if a participant experiences a treatment-related dermatologic AE. If collected, the sample will be shipped to a central laboratory and may be analyzed for histopathology and potentially for molecular markers. Specific instructions on collection and shipping of samples will be provided in a separate laboratory manual

Table 11: Recommended Dose Interruption and Management of Treatment-related Dermatologic Adverse Events

Toxicity Grade (CTCAE v5.0)	Maculopapular Rash	Pruritus/Urticaria	Eczema	Dry Skin[a]
Grade 1	• **Continue treatment with study drug** • Treat with mid- to high-potency topical corticosteroid bid	• **Continue treatment with study drug** • Treat with cooling lotions containing menthol and/or camphor • Treat with mid- to high-potency topical corticosteroid bid	• **Continue treatment with study drug** • Treat with mid- to high-potency topical corticosteroid bid	• **Continue treatment with study drug** • Apply moisturizing creams/lotions without fragrances/irritants (eg, Oncoderm Body Rx spray; Eucerin original)
Grade 2	• **Continue treatment with study drug** • Treat with high-potency topical corticosteroid 1-2 times per day • Treat with anti-H1 therapy (if rash is associated with symptoms such as pruritus and/or urticaria) or GABA agonists • Standardized photographs[b] • Dermatologic consultation recommended	• **Continue treatment with study drug** • Treat with high-potency topical corticosteroid bid • Initiate anti-H1 therapy or GABA agonists • Standardized photographs[b] • Dermatologic consultation recommended	• **Continue treatment with study drug** • Treat with high-potency topical corticosteroid bid • Treat with anti-H1 therapy or GABA agonists (if eczema associated with pruritis) • Standardized photographs[b] • Dermatologic consultation recommended	• **Continue treatment with study drug** • Apply moisturizing creams/lotions without fragrances/irritants (eg, Oncoderm Body Rx spray; Eucerin original)
Grade 3	• **Hold treatment with study drug** • Check CBC/differential-evaluate for eosinophilia • Standardized photographs[b]	• **Hold treatment with study drug** • Standardized photographs[b] • Refer for dermatologic consultation and obtain skin biopsy	• **Hold treatment with study drug** • Standardized photographs[b]	• **Hold treatment with study drug** • Use mid-potency topical steroid (eg, triamcinolone acetonide 0.1%) bid

Toxicity Grade (CTCAE v5.0)	Maculopapular Rash	Pruritus/Urticaria	Eczema	Dry Skin[a]
	• Refer for dermatologic consultation and obtain skin biopsy • Treat with oral corticosteroids **following dermatologic evaluation** (prednisone 0.5 mg/kg/day) for 10-14 days • **Once AE resolves to Grade ≤1, may resume study drug at 1 dose level reduction**	• Consider anti-IgE antibody **following dermatologic evaluation** • **Once AE resolves to Grade ≤1, restart study drug at 1 dose level reduction**	• Refer for dermatologic consultation and obtain skin biopsy • Treat with oral corticosteroids **following dermatologic evaluation** (prednisone 0.5 mg/kg/day) for 10-14 days • Consider interleukin-4 receptor alpha antagonist **following dermatologic evaluation** • **Once AE resolves to Grade ≤1, restart study drug at 1 dose level reduction**	**PLUS** moisturizing creams/lotion without fragrances/irritants (eg, Oncoderm Body Rx spray; Eucerin original) • **Once AE resolves to Grade ≤1, restart study drug at 1 dose level reduction**

Abbreviations: AE=adverse event; bid=twice daily; CBC=complete blood count; CTCAE=Common Terminology Criteria for Adverse Events; GABA=gamma-aminobutyric acid; H1=histamine-1; IgE=immunoglobulin E.

[a] Source: Lacouture et al, 2021

[b] Guidance for standardized photographs will be provided separately

9.7. Study Drug Compliance

To ensure study drug compliance, the Investigator or designee must supervise all study drug dosing that occurs at the site. At each visit, site personnel must review that the participant is compliant with study drug dosing by reviewing the dosing diary and remind the participant of study drug dosing requirements. Compliance must also be assessed by ongoing study drug count.

If a participant demonstrates continued noncompliance of study drug dosing despite educational efforts, the Investigator must contact the Sponsor to discuss discontinuation of the participant from the study.

9.8. Study Drug Accountability

The study center is required to maintain drug accountability records that indicate the study drug's delivery date to the site, inventory of study drug at the site, study drug dispensed to each participant, and study drug returned to the Sponsor or destroyed at site. Accountability records must include dates, quantities, lot numbers, and participant numbers. Sponsor or its designee will review drug accountability records at the site during monitoring visits.

9.9. Study Drug Handling and Disposal

Participants must be instructed to bring all empty, partially used, and full study drug bottles to each clinic visit. The site staff or pharmacy personnel (as appropriate) must retain all materials until returned to the Sponsor or its designee, or sent for destruction according to the site's standard procedure.

9.10. Concomitant Medications and Therapies

All intercurrent medical conditions should be treated by the Investigator according to current community standards of care. Participants may also receive medications for symptomatic relief (eg, analgesics, laxatives, anti-emetics).

9.10.1. Permitted Medications and Therapies but Used with Caution

The following medications should be taken with caution:

- [redacted]
- [redacted]
- [redacted]
- Medications that **may possibly** prolong the QT interval (see Appendix 1)

9.10.2. Prohibited Medications and Therapies

The following medications, substances, and procedures are prohibited during study treatment:

- Initiation of any other anti-tumor therapy for TGCT, including radiation or surgery
- Investigational therapy or investigational procedures of any kind

- The use of intra-articular steroid injections for treatment of TGCT; use of intra-articular steroids for non-TGCT condition is permitted
- Acetaminophen usage exceeding 3 g/day
- Proton-pump inhibitors: discontinue at least 4 days prior to the first dose of study drug
- Medications that are BCRP or OCT2 substrates: discontinue at least 4 days or 5×half-life (whichever is longer) prior to the first dose of study drug
- Medications with a **known risk** of prolonging the QT interval: discontinue at least 14 days or 5×half-life (whichever is longer) prior to the first dose of study drug (see Appendix 1)
- Prophylactic use of myeloid growth factors (eg, G-CSF, GM-CSF)

10. DISCONTINUATION OF STUDY TREATMENT AND PARTICIPANT DISCONTINUATION

10.1. End-of-Treatment

A participant is free to withdraw from the study drug treatment for any reason and at any time without giving reason for doing so and without penalty or prejudice. The Investigator is also free to terminate a participant's study drug treatment at any time if the participant's clinical condition warrants it. The primary reason for treatment discontinuation must be determined using the following categories:

- Protocol Violation
- Progressive Disease by IRR
- Progressive Disease by Investigator Assessment
- Noncompliance with Study Drug
- Adverse Event
- Death
- Withdrawal by Participant (Treatment Discontinuation)
- Physician's Decision
- Pregnancy
- Lost to Follow-up
- Study Terminated by Sponsor
- Other (Any other reason that in the opinion of the Investigator, would justify removing the participant from the study drug, based on the best interest of the participant)

Refer to schedule of assessments for data to be collected at the time of treatment discontinuation, follow-up, and for any further evaluations that need to be completed. Additional information relating to treatment discontinuation due to disease progression is provided in Section 10.5.

10.2. End of Study

A participant is considered to have completed the study if s/he has completed Part 1, Part 2, and all Follow-up visits (Safety Follow-up and Disease Follow-up) of the study.

The primary reason for discontinuation or withdrawal of a participant from the study must be determined using the following categories:

- Completed
- Completed (After Early Treatment Discontinuation)
- Progressive Disease by IRR
- Progressive Disease by Investigator Assessment

- Subsequent TGCT Therapy and/or Surgery
- Death
- Withdrawal by Participant (Withdrawal of Consent)
- Lost to Follow-up
- Physician's Decision
- Study Terminated by Sponsor
- Other (Any other reason that in the opinion of the Investigator, would justify removing the participant from the study, based on the best interest of the participant)

If a participant voluntarily withdraws from the study, the Investigator should attempt to contact the participant to determine the reason(s) for withdrawal. No additional study procedures will be performed and no study-related information will be collected after the participant withdraws consent for this study.

10.3. Replacement of Participants

Participants will not be replaced in this study.

10.4. Lost to Follow-up

A participant will be considered lost to follow-up if both of the following occur:

- Participant misses 2 consecutive study visits and is subsequently unable to be contacted by phone call (3 documented attempts by phone within 2 weeks following the second missed visit)
- Participant does not respond within 2 weeks to a registered letter sent after the 3 attempted phone contacts

10.5. Disease Progression

Part 1 Double-blind

Participants randomized to placebo in Part 1

Participants randomized to placebo with confirmed disease progression by IRR in Part 1 are eligible for crossover to receive open-label vimseltinib in Part 2. Once disease progression is confirmed by IRR, the participant will be unblinded and will follow End of Part 1 assessments outlined in Table 1. After unblinding, the participant may start the crossover procedures on Cycle 1 Day 1 crossover. If the participant declines to continue to Part 2, then the participant will discontinue, complete EOT assessments, and Safety Follow-up Visit as described in Table 1. Disease Follow-up is not required.

Participants randomized to vimseltinib in Part 1

Participants randomized to vimseltinib with confirmed disease progression by IRR in Part 1 will discontinue treatment, complete EOT assessments, and Safety Follow-up Visit as described in Table 1. Disease Follow-up is not required.

Part 2 Open Label

Participants with disease progression will discontinue treatment and complete EOT assessments and Safety Follow-up as described in Table 2 and Table 3. Disease progression must be confirmed by IRR until Week 96 (ie, 2 years after first dose of study drug). Disease Follow-up is not required.

11. STUDY ASSESSMENTS AND PROCEDURES

11.1. Informed Consent Form

Each participant must sign and date a study-specific ICF before any study-specific procedures are performed. The ICF will comply with all applicable regulations governing the protection of participants. An ICF, approved by the Sponsor and the site's Institutional Review Board (IRB), must be used. The Investigator or designee must document the consenting process, including the date when the ICF was signed in the participant's source documents.

Additional information for written consent is provided in Section 13.3.2.

11.2. Randomization/Assigning Participant Number

A unique participant identification number (participant number) will be assigned to each participant once informed consent is obtained. Detailed instructions on assigning participant numbers will be provided in the IRT Manual. If a participant is rescreened, the participant retains the original participant number (see Section 8.6).

11.3. Pre-screening, As Applicable

Participants who require a biopsy to confirm TGCT diagnosis should sign a pre-screen consent form before the biopsy (refer to Section 11.9.2).

11.4. Screening

Screening must occur within 42 days prior to the first dose of study drug to confirm that participants meet the selection criteria for the study. The assessments to be conducted at screening are provided in Table 1. Participants will be enrolled in the study after confirmation of all eligibility criteria and will be randomized to a treatment arm.

11.5. Treatment Period

Duration of treatment is defined in Section 7.4. Treatment period begins when the first dose of study drug is administered in the clinic on Cycle 1 Day 1 in Part 1. Study visits during the treatment period will occur as shown in Table 1, Table 2, and Table 3. All visits must occur within the windows specified.

11.5.1. End of Part 1 Visit

The End of Part 1 visit and the first Part 2 visit both occur at Week 25. The End of Part 1 visit serves as both the last visit of Part 1 and entry into Part 2. **The following assessments for the End of Part 1 visit must be performed before unblinding: MRI, ROM, AE Review, Investigator questionnaires, and PRO questionnaires as noted below in** Table 12. All End of Part 1 assessments must be completed before dosing in Part 2. After unblinding, the assessments to be completed at the first Part 2 visit are shown in Table 13.

Participants who are unblinded in Part 1 due to confirmed disease progression by IRR and were on placebo will cross over to Part 2, and will need to complete End of Part 1 Assessments per

Table 1. The MRI, ROM assessment, and PRO questionnaires will not need to be repeated if completed within 30 days of End of Part 1 Visit.

Table 12: End of Part 1 Visit

End of Part 1 / Week 25	
Assessments	**Timing**
• MRI of affected joint[a] • ROM assessment[b]	• May utilize -7d window and **must perform while blinded**
• AE review • Completion of Investigator questionnaires (CGIC/CGIS) • PRO questionnaires	• At End of Part 1 visit and **must perform while blinded**
• Review concomitant medications/procedures • Full physical exam • Vital signs and weight • Pregnancy test[c] • Collection of central safety labs[d] • Urinalysis • 12-lead ECG	• Must be completed before dosing in Part 2, may be performed while blinded or after unblinding

Abbreviations: AE=adverse event; CGIC=clinician global impression of change; CGIS=clinician global impression of severity; d=day; ECG=electrocardiogram; MRI=magnetic resonance imaging; PRO=patient-reported outcome; ROM=range of motion.
[a] Confirmation that MRI has been performed satisfies unblinding criteria.
[b] ROM assessment (active and passive) of both the affected joint and non-affected joint will be performed at the End of Part 1 visit.
[c] Pregnancy testing must be done within 3 days of dosing in Part 2.
[d] Safety labs to be completed within 3 days of dosing in Part 2
Note: All of the above procedures must be completed as outlined above before dosing in Part 2.

Table 13: First Part 2 Visit

Week 25 **Cycle 1 Day 1 Crossover** For participants crossing over from placebo		**Week 25** **Cycle 7 Day 1** For participants who were assigned vimseltinib in Part 1
• Predose PK and pharmacodynamic sampling • Participant dosing diary instruction/review • Narcotics analgesic diary instruction/review • Vimseltinib dosing • 2 hour postdose PK	**OR**	• Predose PK and pharmacodynamic sampling • Participant dosing diary instruction/review • Narcotics analgesic diary instruction/review • Vimseltinib dosing

Abbreviation: PK=pharmacokinetics

11.6. End-of-Treatment Visit

Part 1 Double-blind

Participants who discontinue study drug in Part 1 should return for an EOT visit within 7 days of the decision to stop study drug and should complete EOT assessments **as outlined in Table 1**. The MRI and ROM assessments will not need to be completed if performed within the previous 30 days.

Part 2 Open Label

Participants who discontinue study drug should return for an EOT visit within 7 days of the decision to stop study drug. At a scheduled clinic visit, if treatment is not given and it becomes evident that open-label study drug will be discontinued, this visit may become the EOT visit.

11.7. Safety Follow-up Visit

Participants will be required to attend a clinic visit 30 days (±5 days) after receiving their last dose of study drug or before the start of new TGCT therapy (including radiation or surgery), whichever occurs first. If a participant has been off study drug for more than 30 days at the time of decision to stop treatment, then the Safety Follow-up Visit will be conducted at the EOT visit. The assessments to be conducted at these visits are provided in the relevant schedule of assessments.

11.8. Disease Follow-up

All participants who discontinue from study treatment for reasons other than radiologically confirmed disease progression or withdrawal of consent will be followed to obtain information about disease status. Participants who discontinue study treatment due to radiologically confirmed disease progression will not need to complete Disease Follow-up. The first disease follow-up will begin 12 weeks (±4 weeks) after the last dose of study drug and an MRI will be required at this visit.

All subsequent disease follow-up will be conducted by telephone every 16 weeks (±4 weeks) thereafter and a review of the participant's medical records for disease status changes will be performed. Disease follow-up will continue for up to 2 years after last dose of study treatment or until radiological progression, start of new subsequent therapy/surgery, or withdrawal of consent. Any SAE occurring during this follow-up period must be reported if assessed as related to study drug by the Investigator.

Information to be collected will include:

- Date of contact
- Status of disease (ie, radiological disease progression, yes/no)
- Date of progression
- Subsequent TGCT therapy and/or surgery (refer to Section 11.9.11)

11.9. Study Procedures

All study procedures will be conducted as shown in Table 1, Table 2, and Table 3.

11.9.1. Demographic/Medical History/Baseline Signs and Symptoms

Data collected will include general participant demographic information (participant's year of birth, age, gender, and race), relevant medical history, and details of prior TGCT therapy, if applicable.

The medical history shall include a complete review of systems, past medical and surgical histories, and any allergies. Medical history includes any significant conditions or diseases that stopped at or prior to informed consent. Ongoing conditions are considered concurrent medical conditions; if possible, the start date and grade for these comorbidities must be documented. Baseline signs and symptoms related to TGCT should also be documented (ie, joint pain, swelling).

11.9.2. Confirmation of Tenosynovial Giant Cell Tumor Diagnosis

A histopathological report confirming TGCT diagnosis must be available prior to randomization. If a prior histopathology report is not available in the medical record, a biopsy of the tumor must be performed to confirm TGCT diagnosis and eligibility as described in Section 11.3.

Participants who require a biopsy to confirm TGCT diagnosis should sign a pre-screen consent form before the biopsy. TGCT diagnosis must be confirmed by a local pathologist prior to randomization. The screening MRI must be performed at least 30 days **after** the biopsy to allow for adequate healing of the biopsy site and accurate tumor measurement.

11.9.3. Assessment of Pain and Stiffness Symptoms

To meet eligibility, participants must have symptomatic disease with at least moderate pain or at least moderate stiffness. Both of these symptoms should be assessed using scales provided by the Sponsor. Moderate pain or stiffness is defined as at least a 4 out of 10, with 10 describing the worst condition. During screening, both assessments should be documented in the medical records.

11.9.4. Surgical Assessments

The surgical assessment questionnaire will be provided by the Sponsor and completed by a qualified person (eg, orthopedic surgeon) to document a participant's surgical status at screening (ie, surgical risk, complexity of surgery, probability of complete resection). The surgical assessment questionnaire may be completed based on an orthopedic consultation/clinic visit that was performed within 6 months prior to screening, provided the participant received no treatment for TGCT in the interim. After screening, surgical assessment questionnaire should also be completed prior to surgery for participants who proceed to surgery during the study, to capture post-treatment status.

11.9.5. Physical Examination

A full physical examination should be performed at screening and at End of Part 1 visit.

At all other study visits, including EOT visit, physical examinations will be abbreviated and driven by clinical findings and/or participants complaints.

11.9.6. Vital Signs, Weight, and Height

Vital sign measurements will be collected after the participant has been at rest for at least 5 minutes. Vital signs will include sitting blood pressure, heart rate, respiratory rate, and temperature. On days when PK sampling is performed, vital sign measurements should be obtained after ECG and prior to the PK sampling timepoint.

Weight will be collected at all study visits.

Height will only be obtained at screening.

11.9.7. Pregnancy Test

Pregnancy test will be performed at the site in all female participants of childbearing potential. A negative serum β-hCG test is required at screening. A negative serum or urine test will be performed within 3 days of the first dose at Cycle 1 Day 1 and Cycle 1 Day 1 crossover. At subsequent clinic visits, pregnancy tests will be performed by serum or urine testing through Week 49. After Week 49, serum or urine tests will be performed monthly. In between clinic visits, pregnancy testing may be performed at home. If pregnancy testing is performed at home, then the Investigator should contact the participant to confirm pregnancy result. Refer to the relevant schedule of assessments for timing of pregnancy testing. If urine pregnancy test result is positive, the study drug must be held and a confirmation serum pregnancy must be performed. If pregnancy is confirmed by serum test, refer to Section 11.9.14.4.2 for information on pregnancy reporting and study withdrawal.

11.9.8. Hepatitis B/C Test

Serology testing for hepatitis B and C at screening will be performed by a central laboratory. Hepatitis B results will include hepatitis B surface antigen (HbsAg), hepatitis B core antibody (anti-HBc), and hepatitis B surface antibody (anti-HBs). Guidance on interpretation of hepatitis B test results will be per Centers for Disease Control and Prevention (CDC) guidelines (CDC, 2020). Hepatitis C results will include hepatitis C virus antibody (anti-HCV).

11.9.9. Prior and Concomitant Medications and Procedures

Prior medications including prescription and nonprescription medications, vitamins, and supplements, and nondrug therapies or procedures taken or performed within 30 days before first dose of study drug will be recorded as prior medications.

Concomitant mediations include any medication as described above (except study drug) taken from first dose of study drug through Safety Follow-up (ie, 30 days after last dose). The type, dose, and route of administration must be documented in the medical records.

11.9.10. Narcotic Analgesic Use

The use of narcotic analgesics will be collected in a patient diary beginning at screening for 1 year (through Cycle 12/Cycle 6 Crossover) or until EOT, whichever comes first. The medication, date, time, number of tablets/patches and total dose for each administration will be recorded.

Examples of narcotic analgesics are:

- Acetaminophen with codeine
- Codeine
- Fentanyl
- Hydrocodone-acetaminophen
- Hydromorphone
- Morphine sulfate
- Oxycodone
- Oxycodone with acetaminophen
- Tramadol

11.9.11. TGCT Treatment and/or Surgery After Treatment Discontinuation

Any new TGCT therapies (systemic or radiation) and/or surgery since discontinuation of study treatment must be recorded. The new TGCT therapy and/or surgery must be noted including details such as the date of surgery, reason for surgery and outcome of surgery or start date of new TGCT therapy.

11.9.12. Collection of Photographic Images of the Affected Joint

A photographic image of the affected joint will be collected, if site agrees and is allowed per IRB/Independent Ethics Committee (IEC)/ Research Ethics Board (REB) and patient consents, at screening and if visual improvement or worsening of swelling is evident during study participation. Images will be taken at the same location at screening and throughout the study. If taken, the images will be shared with the Sponsor. The data will be used as a supplement for disease assessment and may be included in publication for scientific conferences or in the literature. Participants with identifiable marks (eg, birth marks and tattoos) close to the affected joint will not take part.

11.9.13. Efficacy Assessments

Efficacy assessments will be conducted as shown in Table 1, Table 2, and Table 3.

For participants on placebo continuing to Part 2, the efficacy assessment performed for the End of Part 1 visit will serve as both the last assessment of Part 1 and as the baseline assessment used for Part 2.

11.9.13.1. Imaging for Response Assessments

TGCT participants will have an MRI of their affected joint according to the Schedules of Assessments. Tumor response will be assessed by the Investigator using RECIST v1.1 and assessed by an independent radiological reviewer(s) designated by the Sponsor using RECIST v1.1 (see Appendix 3). Modified RECIST (mRECIST; see Appendix 4), TVS (see Appendix 5), and TDS (see Appendix 6) will be generated by the central imaging vendor. Central review is performed for all MRI imaging performed for 2 years after first dose of study drug, after which the images will be read by the site. During the 2 years that IRR is required,

images will not be read in real time by the IRR vendor and tumor responses will not be shared with the Investigators unless a suspected local radiological disease progression is reported by the Investigator for expedited IRR.

A separate Imaging Manual will be provided by the central imaging vendor. The Manual will provide instructions for site training, secure transfer of images to the central vendor, parameters for images acquisition and MRI image Quality Control (QC) process.

During screening, the baseline MRI image will be sent to the central vendor to qualify the participant. All baseline images are required to pass acceptance criteria including eligibility criteria in order for the participant to be randomized. The vendor will provide documentation that the image has passed acceptance criteria and met eligibility criteria. If the image is found not acceptable per the parameters in the manual, a repeat MRI will be required.

For 2 years after first dose of study drug, a similar QC process will be followed for all MRI images. If the image is found not acceptable per the parameters in the manual, a repeat MRI will be requested.

If an Investigator suspects disease progression during the period of 2 years after first dose of study drug, an MRI should be immediately submitted to the central imaging vendor with a request for an expedited read for potential disease progression to determine eligibility to crossover to Part 2 or to discontinue study drug as described in Section 10.5.

11.9.13.2. Range of Motion Assessment

The ROM of the affected and contralateral non-affected joint will be assessed using goniometry according to the relevant schedule of assessments. The modality of assessment will be active, ie, measuring a motion produced by the participant's voluntary, unassisted muscle contraction, and passive, ie, measuring a motion produced by the application of external force by an examiner. Active and passive assessments of the affected joint will be performed at screening and thereafter according to the relevant schedule of assessments. Active and passive assessments of the non-affected contralateral joint will only be performed at screening and End of Part 1 visit.

The joint, side of body, motions assessed, and degrees measured (the start and end position of motion) will be recorded for active and passive motion. Results should be documented on the ROM form provided by the Sponsor. Adequately trained site personnel (physiotherapist or orthopedic surgeon) who are blinded to study treatment should perform the ROM assessment. Every effort should be made to have the same assessor conduct all ROM assessments for each participant throughout the protocol. All motions applicable to a specific joint should be collected for the duration of the clinical study.

11.9.14. Safety Assessments

Safety assessments will be conducted as shown in Table 1, Table 2, and Table 3.

11.9.14.1. Electrocardiogram

Electrocardiograms will be performed according to the relevant schedule of assessments.

For each ECG timepoint, single 12-lead ECGs will be obtained using a local ECG machine. ECG intervals (QT, RR, QTcF, HR, and QRS) will be collected. Unscheduled, single 12-lead ECGs may be obtained by the site at any time during the study if clinically indicated.

11.9.14.2. Clinical Laboratory Tests for Safety

Clinical laboratory tests are summarized in Table 14 and will be performed by a central laboratory, except for urinalysis, according to the relevant schedule of assessments. Additional (unscheduled) local laboratory samples for safety or repeat tests may be collected, if clinically indicated.

All laboratory test results that are abnormal and considered clinically significant must be reported as AEs (Section 11.9.14.3.1). If a clinically significant laboratory AE is supported by a corresponding local lab result, but not by the central lab result, the local lab result will be recorded. All samples will be collected in accordance with acceptable laboratory procedures and graded for toxicity as defined by the National Cancer Institute (NCI)-CTCAE, v5.0.

Available local laboratory test results should be used for treatment management decisions and initial assignment of CTCAE grading. Every effort should be made to discuss any changes to study drug dosing with the Sponsor before implementation, and only if not feasible beforehand, to inform the Sponsor within the same day. Central laboratory results will be used for final assignment of CTCAE grading. In the case of different grades associated with local versus central laboratory results for AEs, the Investigator should determine which laboratory values will be used to document grading of AEs. The local vs central laboratory result with the highest grade should be considered to document grading of AEs.

Table 14: Clinical Laboratory Tests

Hematology	Coagulation	Chemistry	Urinalysis (dipstick)[a]
Hematocrit Hemoglobin Platelet count Red blood cell count White blood cell count with differential	Activated partial thromboplastin time Prothrombin time International normalized ratio	Alanine aminotransferase Albumin Alkaline phosphatase Aspartate aminotransferase Bicarbonate Calcium Cholesterol Chloride Creatine phosphokinase Creatinine Gamma-glutamyl transferase Glucose Potassium Sodium Magnesium Phosphorus Total bilirubin Conjugated (direct) bilirubin Unconjugated (indirect) bilirubin[b] Total protein Triglycerides Blood urea nitrogen	Hemoglobin Glucose Ketone Protein Specific gravity

[a] An additional microscopic examination will be performed if any dipstick analytes are 2+ or higher. A participant should undergo further assessment (eg, a 24-hour urine collection) if the protein analyte is ≥2+.
[b] Will be calculated by central laboratory.

11.9.14.3. Adverse Events and Serious Adverse Events

11.9.14.3.1. Adverse Event

An AE is any untoward medical occurrence in a clinical study participant. The occurrence may or may not have a causal relationship with the investigational treatment. This includes any newly occurring event or previous condition that has increased in severity or frequency after the ICF is signed.

Illnesses present prior to the participant signing the ICF are considered to be pre-existing conditions and are documented on the medical history eCRF. Pre-existing conditions that worsen during the study are entered on the AE eCRF.

Pregnancy is not considered an AE, although a participant will be withdrawn from the study if a pregnancy occurs. The pregnancy, including a partner's pregnancy, must be reported to Deciphera or designee, and additional follow-up may be required as described in Section 11.9.14.4.2.

11.9.14.3.2. Serious Adverse Event

An SAE is any AE, occurring at any dose and regardless of causality, that:

- Results in death (ie, the adverse event causes or leads to death)
- Is life threatening. The participant is at immediate risk of death from the reaction as it occurs. This does not include reaction that, had it occurred in a more severe form, might have caused death
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity (eg, a substantial disruption of a person's ability to conduct normal life functions)
- Results in a congenital anomaly/birth defect
- An important medical event that may not result in death, be immediately life threatening, or require hospitalization may be considered to be an SAE when, based upon appropriate medical judgment, the event may jeopardize the participant and may require intervention to prevent one of the other outcomes listed above

Admission to a hospital or an inpatient unit for a nonmedical reason (ie, social stay admission) during the study in the absence of untoward medical occurrence will not be considered as an SAE but will be captured as an AE.

Hospitalization due to worsening of pre-existing conditions should be reported as an SAE.

Clarification must be made between the terms "serious" and "severe", because they are not synonymous. 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 a severe headache. This is not the same as "serious," which is based on participant/event outcome or action criteria described above and is usually associated with events that pose a threat to a participant's life or functioning. Seriousness, not severity, serves as a guide for defining regulatory reporting obligations.

11.9.14.3.3. Relationship to Study Drug

The assessment of the study drug relationship to each AE will be documented based on the temporal relationship and the best clinical judgment of the Investigator. Causality will be determined using the 2 categories below. All study drugs are considered when defining causality.

- **Related:** The AE is known to occur with the study drug or there is a reasonable possibility that the study drug caused the AE, and there is a temporal relationship

between the study drug and event that supports relatedness. Reasonable possibility means that there is evidence to suggest a causal relationship between the study drug and the AE.

- **Not Related:** There is no reasonable possibility that the treatment with study drug caused the event, the temporal relationship between the study drug and event onset does not support relatedness, or an alternate etiology has been established.

11.9.14.3.4. Severity Assessment

The Investigator must determine and record the severity of all serious and nonserious AEs. The NCI-CTCAE, v5.0, must be used for grading the severity of AEs (NCI-CTCAE, 2020).When there is a change in severity of an existing adverse event including improvement or worsening of an event, a new AE should be reported.

The severity of an AE that does not appear in the CTCAE scale must be determined according to Table 15.

Table 15: Severity Grading Scale

Classification	Definition
Grade 1 (Mild)	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
Grade 2 (Moderate)	Minimal, local, or noninvasive intervention indicated; limiting age-appropriate instrumental Activities of Daily Living.
Grade 3 (Severe)	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care Activities of Daily Living.
Grade 4 (Life threatening)	Life-threatening consequences; urgent intervention indicated.
Grade 5 (Death)	Death related to AE.

Abbreviation: AE=adverse event

11.9.14.3.5. Study Drug Action Taken

The Investigator must classify the study drug action taken with regard to the AE. The action taken must be classified according to the categories shown in Table 16.

Table 16: Classification for Study Drug Action Taken With Regard to an Adverse Event

Classification	Definition
Dose Not Changed	Study drug dose not changed in response to an AE.
Dose Reduced	Study drug dose reduced in response to an AE.
Drug Interrupted	Study drug administration interrupted in response to an AE.
Drug Withdrawn	Study drug administration permanently discontinued in response to an AE.

Classification	Definition
Not Applicable	Action taken regarding study drug administration does not apply. "Not applicable" must be used in circumstances such as when the study drug had been completed before the AE began and no opportunity to decide whether to continue, interrupt, or withdraw study drug is possible.

Abbreviation: AE=adverse event

11.9.14.3.6. Adverse Event Outcome

All AEs will be followed until resolution, until deemed stable by the Investigator, or until the participant is deemed by the Investigator to be lost to follow-up or the participant completed the safety follow-up period. For the purposes of study analysis, if the event has not resolved at the end of the study reporting period, it must be documented as ongoing.

The outcome must be classified according to the categories shown in Table 17.

Table 17: Adverse Event Outcome Definition

Classification	Definition
Recovered/Resolved	Resolution of an AE with no residual signs or symptoms.
Recovered/Resolved with Sequelae	Resolution of an AE with residual signs or symptoms.
Recovering/Resolving	Improvement of an AE.
Not Recovered/Not Resolved (Continuing)	Either incomplete improvement or no improvement of an AE, such that it remains ongoing.
Fatal	Outcome of an AE is death. "Fatal" must be used when death is related to the AE.
Unknown	Outcome of an AE is not known (eg, a participant lost to follow-up).

Abbreviation: AE=adverse event

11.9.14.3.7. Treatment Given

The Investigator must ensure adequate medical care is provided to patients for any AEs. In addition, the Investigator must describe whether any treatment was given for the AE. "Yes" is used if any treatment was given in response to an AE and may include treatments such as other medications, hospitalization, surgery, or physical therapy. "No" indicates the absence of any kind of treatment for an AE.

11.9.14.3.8. Additional Points to Consider for Adverse Event

11.9.14.3.8.1. Clinically Significant Assessments

Study assessments including laboratory tests, ECGs, physical examinations, and vital signs must be assessed and those deemed as clinically significant must be documented as an AE. When possible, a clinical diagnosis for the study assessment must be provided rather than the abnormal test result alone (eg, urinary tract infection, anemia). In the absence of a diagnosis, the abnormal study assessment itself may be listed as the AE (eg, bacteria in urine or decreased hemoglobin).

An abnormal study assessment is considered clinically significant if the patient has 1 or more of the following:

- Worsening, from baseline, concomitant signs or symptoms related to the abnormal study assessment
- Further diagnostic testing or medical/surgical intervention is required
- A change in the dose of study drug, if study drug is withheld, or discontinuation from study drug occurs

Repeat testing to determine whether the result is abnormal, in the absence of any of the above criteria, does not necessarily meet clinically significant criteria. The determination of whether the study assessment results are clinically significant must be made by the Investigator.

A laboratory abnormality judged to be Grade 4, in itself, may not constitute an SAE unless the clinical status of the patient indicates a life-threatening AE.

Symptoms of the disease under study must not be recorded as AEs as long as they are within the normal day-to-day fluctuation or expected progression of the disease, including significant worsening unless the deterioration was unexpected, and are part of the efficacy data to be collected in the study.

11.9.14.3.9. Monitoring and Recording Adverse Events

The AE (including SAEs) reporting period will begin after a participant signs the main ICF and will continue until completion of the Safety Follow-up Visit or 30 days after the final dose of study drug. Any SAE having an onset after the Safety Follow-up Visit will not be collected or reported unless the Investigator feels that the event may be related to the study drug. Only SAEs that are assessed by the Investigator as related to the biopsy will be collected after a participant signs the pre-screening consent and until the participant has signed the main ICF.

Participants will be instructed by the Investigator or designee to report the occurrence of any AE. All volunteered, elicited, and observed AEs are to be recorded.

If a participant begins a new TGCT therapy, the safety reporting period ends at the time the new treatment is started; however, death must always be reported when it occurs during the safety reporting period irrespective of intervening treatment.

The Investigator will assess all AEs regarding any causal relationship to the study drug, the intensity (severity) of the event, action taken, and participant outcome (see Section 11.9.14.3).

11.9.14.4. Reporting Adverse Events

11.9.14.4.1. Reporting of Serious Adverse Events

The written report for SAEs should be submitted on the SAE form provided for this purpose. The SAE report must include the Investigator's opinion as to whether the event is study drug related. If this relationship is determined to be related to study drug, evidence to support this assessment must also be provided.

For clinical study safety reporting purposes, the applicable version of the IB will be used as the reference document to designate event expectedness.

All SAEs that occur within the reporting period, regardless of causality, must be reported by the Investigator to Deciphera via the designee **immediately and no longer than 24 hours** from the point in time when the Investigator becomes aware of the SAE. Serious AEs must be followed until resolution, the condition stabilizes, or the Investigator and Sponsor agree that follow-up is not required. For purposes of regulatory safety monitoring, the Investigator is required to follow the event to resolution and report to the Sponsor the outcome of the event, unless the participant is deemed by the Investigator to be lost to follow-up or the participant completed the safety follow-up period.

If there are suspected unexpected serious adverse reactions (SUSARs) associated with the use of the study drug, the Sponsor or authorized designee will ensure that the appropriate regulatory agencies and all participating investigators are notified on an expedited basis. In addition, the Sponsor or authorized designee will be responsible for notification of SUSARs to the ethics committees. It is the responsibility of the Investigator to promptly notify the local IRB/IEC/ REB of SUSARs according to the institutional policy. An unexpected event is one that is not reported in the IB. Disease progression is not considered an AE. If AEs/SAEs occur in relation to disease progression that are not consistent with the nature and natural progression of the participant's disease, these AEs/SAEs must be reported per AE/SAE reporting requirements in this section.

11.9.14.4.2. Reporting of Pregnancy

The written report for pregnancies in female participants and in female partners of male participants should be submitted on the Pregnancy Report Form provided for this purpose within 24 hours of awareness of pregnancy.

Pregnancy is not considered an AE, although a female participant will be withdrawn from the study if a pregnancy occurs. Any pregnancy complication that meets the criteria of an SAE must be reported as per Section 11.9.14.4.1. The pregnancy, including a partner's pregnancy, must be reported to Deciphera or designee within 24 hours of site awareness, and additional follow-up may be required. In certain situations, reporting of partner pregnancies may not be necessary if mandated by local IRB/IEC/REB policy/investigative site Standard Operating Procedure.

If the female partner of a male participant becomes pregnant while on study, the male participant must notify the Investigator immediately, and the pregnant female partner should be advised to call her healthcare provider immediately. The male participant must commit to use acceptable methods of contraception (to ensure there is no exposure of the fetus to study drug) for the duration of the study and until 120 days following the last dose of study drug.

If the participant was receiving vimseltinib, the female participant or female partner of the male participant must be followed until the end of the pregnancy and the infant must be followed for 1 year after the birth, provided informed consent is obtained. A separate ICF will be provided to explain these follow-up activities.

11.9.14.4.3. Abuse, Misuse, Overdose, and Medication Error

Adverse events associated with drug abuse, misuse, overdose, or medication error must be reported as per Section 11.9.14.3.

Abuse of a medicinal product: Persistent or sporadic, intentional excessive use of medicinal products, which is accompanied by harmful physical or psychological effects [DIR 2001/83/EC Art 1(16)].

Misuse: Intentional and inappropriate use of a medicinal product not in accordance with the prescribed or authorized dose, route of administration, and/or the indication(s) or not within the legal status of its supply.

Overdose: Administration of a quantity of study drug given per administration or per day, which is above the assigned dose.

Medication Error: An error made in prescribing, dispensing, administration, and/or use of the study drug. Medication errors are reportable to the Sponsor as defined below.

- The dispensing, administration, and/or use of the unassigned study drug.
- The administration and/or use of an expired study drug.

Note: Cases of participants missing doses of the study drug are not considered reportable as medication errors.

11.9.15. Patient-reported Outcome Measures

During the screening period, the participant should complete 14 consecutive days of questionnaires on an electronic device as outlined in Table 4. In order to meet study entry criteria, the participant must complete at least 4 baseline assessments (each) of BPI Worst Pain and Worst Stiffness NRS items, at least one baseline PROMIS assessment, and one baseline 5-level EQ-5D (EQ-5D-5L) assessment. The patient should be encouraged to complete all 14 consecutive days of screening questionnaires to ensure robust baseline data collection for the study PRO endpoints.

11.9.15.1. PROMIS-Physical Function Questions

Physical function will be assessed using 15 questions from the PROMIS-Physical Function (PROMIS-PF) item bank that was developed by the National Institutes of Health. The PROMIS-PF questions will include 2 scales to measure tumor location-specific physical function. The first scale includes 13 questions and is intended for use by participants with lower-extremity tumors (eg, knee). The second scale includes 11 questions and is intended for use by participants with upper-extremity tumors (eg, digits). Nine of the PROMIS-PF questions are overlapping (ie, included in both lower- and upper-extremity scales). The 15 questions use one of two 5-point verbal rating scales: either 1="unable to do", 2="with much difficulty", 3="with some difficulty", 4="with a little difficulty", and 5="without any difficulty"; or 1="cannot do", 2="quite a lot", 3="somewhat", 4="very little", and 5="not at all."

11.9.15.2. Worst Stiffness Numeric Rating Scale

The Worst Stiffness NRS is a single question that asks the participant to assess their worst stiffness in the last 24 hours. Participants rate their worst stiffness on a scale of 0 to 10, where 0 is "no stiffness" and 10 is "worst imaginable."

11.9.15.3. Brief Pain Inventory-Short Form

The Brief Pain Inventory-Short Form (BPI-SF) was developed with support from the NCI and the World Health Organization (WHO). It is a 9-item questionnaire that assesses the severity and impact of pain, across several dimensions. Two questions of the BPI-SF, the worst pain question, which measures pain severity at its worst in the last 24 hours, and the average pain question, which measures average pain, will be used in this study. For both questions, participants rate their pain on a scale of 0 to 10, where 0 is "no pain" and 10 is "pain as bad as you can imagine."

11.9.15.4. EQ-5D-5L

The EQ-5D-5L was developed by the EuroQol Group. The measure assesses 5 areas of functioning and consists of the EQ-5D descriptive system and the EQ Visual Analogue Scale. Answers to the descriptive questions are given by selecting among 5 levels of difficulty, while the Visual Analogue Scale is scored from 0 to 100.

11.9.15.5. GP5 from FACT-G

The GP5 "burden-of-side-effects" question is an item taken from the Functional Assessment of Chronic Illness Therapy (FACIT) FACT-G questionnaire, a validated measure that has been used extensively in clinical studies (FACIT, 2020). It asks participants to indicate how bothered they are by side effects of study treatment on a scale of 0 to 4, where 0 is "Not at all" and 4 is "Very much."

11.9.15.6. Patient Global Impression of Change

Three PGIC questions will be asked of participants. These questions assess the participant's impression of change to the following, since the start of the study: their symptoms at the site of their tumor, ROM at the site of their tumor, and tumor-related physical functioning.

For all 3 questions, participants answer on a scale of 1 to 7, where 1 is "Very Much Improved", 2 is "Much Improved", 3 is "Minimally Improved", 4 is "No Change", 5 is "Minimally Worse", 6 is "Much Worse" and 7 is "Very Much Worse."

11.9.15.7. Patient Global Impression of Severity

Two PGIS questions will be asked of participants. These questions ask the participant to rate the severity of the impact of their tumor on their ROM and the severity of the impact of their tumor on their physical function, at present.

For both questions, participants are asked to select one of the following responses: "None", "Mild", "Moderate", "Severe", or "Very Severe".

11.9.15.8. End of Part 1 Interview

Participants enrolled in the study will participate in one-on-one telephone End of Part 1 interviews, lasting approximately 60 minutes. These interviews will be conducted by a trained interviewer 1 to 28 days prior to End of Part 1 visit (ie, anytime during Cycle 6), before unblinding. The participant interview will be conducted in the countries where an interviewer is available to conduct in local language.

11.9.16. Clinician Reported Outcome Measures

11.9.16.1. Clinician Global Impression of Change

Three CGIC questions will be asked of clinicians. These questions assess the clinician impression of change in the participant's symptoms, ROM, and physical function, since the start of the study.

The CGIC questions use the same scale as the PGIC.

11.9.16.2. Clinician Global Impression of Severity

Two CGIS questions will be asked of clinicians. The questions ask the clinician to rate their impression of the severity of the impact of the tumor on the participant's ROM and the severity of the tumor-related impact on the participant's physical function, at the time of answering the question.

The CGIS questions use the same scale as the PGIS questions.

11.9.17. Exploratory Assessments

Remaining samples (plasma, whole blood, and tumor tissue) will be stored for up to 15 years after the end of the study. These samples may be used for further analysis intended to address scientific questions related to study drug and/or disease. A decision to perform such exploratory research studies will be based on data obtained from vimseltinib clinical studies, new scientific findings related to the drug class or disease, and/or reagent and assay availability.

11.9.17.1. Tumor Tissue

Tumor tissue sample will be collected as available. Any tumor sample collected prior to Cycle 1 Day 1 and within the last 5 years is acceptable.

Procedures relating to tumor tissue collection are described in a separate laboratory manual.

11.9.17.2. Pharmacokinetic Sample Collection

Pharmacokinetic samples will be collected according to the relevant schedule of assessments. All predose samples should be collected within 60 minutes before dosing. Postdose samples should be collected ±30 minutes of nominal timepoint. Samples missed or lost for any reason should be recorded. Actual dates and times of blood collection must be recorded.

Pharmacokinetic samples should be collected after the corresponding ECG and vital signs at the same timepoint.

Upon the occurrence of a severe and unexpected AE in an individual participant that the Investigator decides could be related to study drug, a single, ad hoc PK sample may be collected as deemed medically appropriate by the Investigator and Sponsor. The objective in collecting this PK sample would be to investigate any potential association between PK and the unexpected AE. Pharmacokinetic samples will be analyzed by a central laboratory. Details regarding collection, sample handling and shipping are described in a separate laboratory manual.

11.9.17.3. Pharmacodynamic Sample Collection

The objective of collecting these research samples is to investigate the relationship of biomarkers and the medical condition or disease progression. Pharmacodynamic samples will be collected according to the relevant schedule of assessment tables.

Pharmacodynamic samples will be analyzed by multiple laboratories. Details regarding collection, sample handling and shipping will be described in a separate laboratory manual.

Upon the occurrence of a medical condition in an individual participant that the Investigator feels may be related to study drug (eg, a severe and unexpected toxicity) or if a participant experiences disease progression, an ad hoc pharmacodynamic whole blood and plasma sample may be collected as deemed medically appropriate by the Investigator and Sponsor. Collection of such samples would be infrequent and account for no more than 1 additional timepoint in a 28-day cycle for a given participant. **Asia and Pacific countries only: whole blood sample will not be collected.**

11.9.17.4. Pharmacogenomic Sample Collection

Pharmacogenomic samples will be used to assess germline polymorphisms in genes involved in the metabolism or disposition of vimseltinib. Additionally, the potential relationship between polymorphisms and clinical response and/or study drug-related toxicity will be assessed. A single whole blood sample will be collected prior to dosing for all participants on Cycle 1 Day 1 only.

Details regarding sample collection, processing and shipment will be described in a separate laboratory manual.

11.10. Study Continuation Plan

If a local or national emergency is declared that may impact per-protocol study conduct, then alternative assessments may be implemented after review and approval by the Sponsor to protect participant safety and data quality while minimizing burden.

11.11. Study Termination

When the Sponsor is aware of information on matters concerning the quality, efficacy, and safety of the study drug, as well as other important information that may affect proper conduct of the clinical study, the Sponsor may discontinue the clinical study and send a written notice of the discontinuation along with the reason to the Investigator.

If an Investigator intends to discontinue participation in the study, the Investigator must immediately inform the Sponsor of the discontinuation and the reason for it.

11.11.1. Criteria for Suspension or Premature Termination of the Study

Criteria for either temporary suspension or premature termination of the study include:

1. New information regarding the safety or efficacy of the study drug that indicates a change in the known risk/benefit profile for the compound, such that the risk/benefit is no longer acceptable for participants in the study.

2. Significant violation of Good Clinical Practice (GCP) that compromises the ability to achieve the primary study objectives or compromises participant safety.
3. The Sponsor may suspend or prematurely terminate the study for reasons not related to the conduct of the study.

11.11.2. Criteria for Premature Termination or Suspension of Investigational Sites

A study site may be terminated prematurely or suspended if the site (including the Investigator) is found to be in significant violation of GCP, protocol, contractual agreement, or is unable to ensure adequate performance of the study.

11.11.3. Procedures for Premature Termination or Suspension of the Study or the Participation of Investigational Site(s)

In the event that the Sponsor elects to terminate or suspend the study or the participation of an investigational site, a study-specific procedure for early termination or suspension will be provided by the Sponsor; the procedure will be followed by applicable investigational sites during the course of termination or study suspension.

12. STATISTICS

12.1. Sample Size Determination

The sample size selection of approximately 120 participants with TGCT (n~80 vimseltinib, n~40 placebo) was based on considerations for powering the analyses of the primary endpoint, key secondary endpoints, detection of rare safety events and overall exposure to vimseltinib, and assuming 15% participant dropout. Participants will be randomized in a 2:1 ratio of vimseltinib versus placebo.

This sample size will have 98% power to detect a statistically significant difference between treatment arms, assuming true ORRs of 35% and 5% in the vimseltinib arm and the placebo arm, respectively, using a two-sided Fisher's exact test at a 5% type I error rate level.

12.2. Randomization and Blinding

The study will randomize approximately 120 participants with TGCT in a 2:1 ratio (vimseltinib:placebo). Randomization will be stratified for tumor location (lower limb/all other) and region (U.S./non-U.S.).

Prior to the unblinding of study data, the Sponsor will approve a comprehensive statistical analysis plan (SAP).

Where required, safety personnel at the Sponsor or designee may be unblinded to a participant's study drug assignment to meet reporting requirements to regulatory agencies. In addition, the Investigator, participant, Sponsor, and study team will be unblinded at the time the participant has disease progression by RECIST v1.1 based on IRR.

Additional Sponsor representatives may be unblinded to some data for the purposes of ensuring adequacy of study conduct, including proper distribution of study drug.

At no point in time before official full study unblinding will any aggregate efficacy and safety analyses by true treatment assignment be conducted by the Sponsor or Sponsor representatives, unless there is explicit permission to do so, for instance high level efficacy assessment for the purposes of a DMC review to determine the adequacy of the risk/benefit profile of the drug as it pertains to the conduct of the clinical study.

12.3. Analysis Set

The Screen Set consists of all participants who have signed the ICF.

The Intent-to-Treat (ITT) Set consists of participants who have been randomized to a study treatment regimen. Analysis will be performed according to the allocated treatment regimen. The ITT population will be the primary analysis set for all the efficacy endpoints analyses.

The Per-protocol (PP) Analysis Set consists of participants in the ITT Set with at least one postbaseline tumor assessment who have no important protocol deviations that are expected to compromise the efficacy and/or safety assessments as follows:

- Violations of key inclusion/exclusion criteria
- Noncompliance with study treatment

- Participant taking wrong study treatment
- Participant receiving prohibited medications or therapies

The efficacy analyses performed on the PP Set will be supportive and treatment group will be based on actual treatment received. Participants with deviations resulting in exclusion from the PP Set will be identified and documented prior to database lock.

The Safety Set consists of participants who have received at least one dose of study treatment. Analysis will be performed according to the treatment regimen actually received.

The PK Set consists of participants in the Safety Set who have at least one evaluable postdose PK sample (or nonmissing postdose PK concentration).

The Pharmacodynamic Set consists of participants in the Safety Set who have at least one pharmacodynamic evaluation.

The PRO Set consists of participants in the ITT Set who have valid baseline and at least one postbaseline PRO assessments.

12.4. Statistical Analyses

12.4.1. General Methods

Data collected in this study will be documented using summary tables and participant data listings. Continuous variables will be summarized using descriptive statistics (number of participants, mean, median, standard deviation, minimum, and maximum). Categorical variables will be summarized using frequencies and proportions. Time-to-event data will be summarized via Kaplan-Meier (KM) methodology using the 25^{th}, 50^{th} (median), and 75^{th} percentiles with associated 2-sided 95% confidence intervals (CIs).

Unless specified otherwise, baseline measurements must be the most recent value prior to receiving the first dose of study drug. If an assessment is not available, then the last assessment prior to that visit would be used.

Medical history, AEs, and concurrent procedures will be coded using Medical Dictionary for Regulatory Activities (MedDRA). Prior and concomitant medications will be coded using the WHO Drug Dictionary.

This study will be broken into 2 periods: the randomized blinded period and the open-label portion that occurs after the study treatment unblinding at Week 25.

Unless specified, the ITT and PP sets are used for efficacy analysis and the Safety Set is used for the safety analysis.

12.4.2. Disposition of Participants

Participant disposition will be summarized overall for all participants who entered the study (ie, signed the informed consent for the study). The number and proportion of participants who entered the double-blind part of the study will be displayed. In addition, the number of participants in each analysis set will be presented. The number and proportion of participants who complete the double-blind part of the study, as well as those who complete the open-label

part of the study will be presented. The number and proportion of participants who discontinue the study will be summarized along with the reason for discontinuation.

12.4.3. Demographic and Baseline Characteristics

Demographic and baseline characteristics at study entry will be summarized for the ITT, safety, and PP analysis sets. Medical history will be summarized overall for the Safety Set.

12.4.4. Extent of Exposure

The total number of participants who received study medication will be summarized by frequency and percentage. In addition, the number of cycles received will be displayed using both categorical and continuous descriptive statistics. These summaries will be performed for the Safety Set.

12.4.5. Efficacy Analyses

12.4.5.1. Primary Efficacy Analysis

Objective response rate is defined as the proportion of participants with a CR or a PR based on IRR per RECIST v1.1. Objective response rate at Week 25 will be compared between the 2 treatment arms using a two-sided Cochran-Mantel-Haenszel test stratified by the randomization stratification factors. The test will be performed at a 0.05 alpha level on the ITT set. A 95% CI for the proportion in each arm and for the difference in proportion will be presented.

No confirmation (ie, CR or PR at the subsequent MRI assessment) will be required for a CR or PR per RECIST v1.1 for a randomized study. Complete and partial response will define response for the primary endpoint and additional efficacy analyses.

Determination of an overall response for each timepoint is based on the combination of responses for target lesions, and the presence or absence of one or more new lesions. For this protocol, determination of the tumor response status for each participant in Part 1 with respect to the primary efficacy endpoint is shown in Table 18.

Table 18: Definitions of Response for the Primary Efficacy Endpoint

Response at Week 13	Response at Week 25	End of Part 1 Tumor Response Status (Primary Efficacy Endpoint)
CR or PR	CR	Response (CR)
CR or PR	PD	Non-response (PD)
PR	Non-CR/non-PD/non-NE[a]	Response (PR)[b]
SD	CR or PR	Response (CR or PR)
SD	SD	Non-response (SD)
SD	PD	Non-response (PD)[c]
CR, PR, SD, and NE	NE	Non-response (NE)

Response at Week 13	Response at Week 25	End of Part 1 Tumor Response Status (Primary Efficacy Endpoint)
PD	Any	Non-response (PD)
NE	CR or PR	Response (CR or PR)
NE	SD or PD	Non-response (SD or PD)

Abbreviations: CR=complete response; NE=not evaluated or inevaluable; PD=progressive disease; PR=partial response; SD=stable disease.

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

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

[c] To be considered SD, the tumor must achieve the criteria for SD at the Week 25 visit; shorter duration SD will not be considered SD at the End of Part 1.

12.4.5.2. Secondary Efficacy Analyses

As specified in following the sub-sections, multiple secondary endpoints will be analyzed using a mixed model for repeated measurements (MMRM). The dependent variable will be the change from baseline. Each of these models will include fixed effects for treatment group, timepoint, stratification factor for region (U.S. versus non-U.S.), stratification factor for tumor location, and the baseline value of the corresponding endpoint. For the analysis of ROM only, tumor location will be replaced with joint type (knee, ankle, or other). An unstructured variance-covariance matrix will be used. Statistical comparisons between treatment groups will be made at the specified timepoint.

12.4.5.2.1. Tumor Response by Tumor Volume Score

In addition to being assessed using RECIST v1.1 (primary endpoint), tumor response will also be assessed using TVS. Objective response rate by TVS is defined as the proportion of participants with a CR or PR.

Tumor volume score ORR at Week 25 will be compared between the 2 treatment arms using the same approach used for the primary endpoint analysis.

12.4.5.2.2. Range of Motion

Measurement of the affected and contralateral, non-affected joint will be assessed using a goniometer. The measurement (in degrees) of the affected joint will be used to derive a relative ROM obtained through normalization to the measurement from a reference standard value provided by the American Medical Association per motion and type (active or passive).

At screening, the motion with the smallest relative ROM value (worst) will be identified, and this motion will be used for evaluating the change in relative ROM subsequently. Only the motion with the most impaired ROM at screening will be selected for subsequent analyses. If there are ties, the multiple motions with the same relative ROM value at screening will be identified, and the average of relative ROM values will be calculated at each postscreening visit and be used in the analysis as the single relative ROM value for that specific visit.

The main analysis of relative ROM will consist in a comparison between treatment arms of the mean change from baseline at Week 25 using a MMRM.

The observed value and change from baseline in relative ROM will be listed for each participant, and mean change from baseline will be calculated and presented in table and figure format at each timepoint by treatment group. In addition, such mean changes may be displayed by joint type and/or motion.

An additional analysis of these data will be performed on results normalized to the measurement obtained from the contralateral, non-affected joint.

12.4.5.2.3. Physical Function

The main analysis of PROMIS-PF will consist of a comparison between treatment arms of the mean change from baseline at Week 25 using a MMRM.

The observed value and change from baseline in PROMIS-PF will be listed for each participant, and mean change from baseline will be calculated and presented in table figure format at each timepoint by treatment group.

12.4.5.2.4. Worst Stiffness Numeric Rating Scale

The main analysis of Worst Stiffness NRS will consist of a comparison between treatment arms of the mean change from baseline at Week 25 using a MMRM.

The observed value and change from baseline in Worst Stiffness NRS will be listed for each participant, and mean change from baseline will be calculated and presented in table and figure format at each timepoint by treatment group.

12.4.5.2.5. EQ-5D-5L

The main analysis of the EQ-VAS will consist of a comparison between treatment arms of the mean change from baseline at Week 25 using a MMRM.

The observed value and change from baseline in EQ-VAS will be listed for each participant, and mean change from baseline will be calculated and presented in table and figure format at each timepoint by treatment group.

The EQ-5D-5L will be summarized by frequency and percentage for each level of each dimension by timepoint and treatment group.

12.4.5.2.6. Brief Pain Inventory – Response

A responder analysis based on the BPI Worst Pain NRS item and analgesic use will be performed. A responder will be defined as a participant who: (i) experienced a decrease of at least 30% in the mean BPI Worst Pain NRS item and (ii) did not experience a 30% or greater increase in narcotic analgesic use. The change in BPI Worst Pain NRS for responder assessment will be assessed by comparing data collected during a 14-day period prior to the current visit with baseline values collected prior to the first dose of study drug. This will be referenced as BPI-30 response.

BPI-30 response at Week 25 will be compared between the 2 treatment arms using the same approach used for the primary endpoint analysis.

12.4.5.2.7. Objective Response Rate

Objective response rate per RECIST v 1.1 over the entire study and its corresponding 95% CI will be presented.

12.4.5.2.8. Tumor Response per mRECIST

Response rate by mRECIST at Week 25 will be compared between 2 treatment arms using a two-sided Cochran-Mantel-Haenszel test stratified by the randomization stratification factors at the 0.05 alpha level based on the ITT population. The 95% CI in each arm and the difference, along with its 95% CI, will be presented.

12.4.5.2.9. Patient-reported Outcomes

Change from starting value will be summarized by timepoints. At least 4 measurements for NRS and 4 for BPI are needed across Weeks 2 and 3 for the measurements not to be set to missing. Averages of Weeks 2 and 3 prior to a study visit will be compared to the average values reported during screening.

12.4.6. Safety Analyses

Participants from the Safety Set will be included in safety analyses.

AEs will be coded using the MedDRA for purposes of summarization. All AEs occurring on study will be listed in by participant data listings. Treatment-emergent AEs will be tabulated, where treatment emergent is defined as any AE that occurs after administration of the first dose of study drug and through 30 days after the last dose of study drug. Tabulations for all TEAEs, treatment-emergent SAEs, related TEAEs, dose reduction, dose interruptions, and discontinuation of study drug due to AE will be produced. By participant listings will be provided for deaths, SAEs, and AEs leading to discontinuation of study drug.

Change from baseline in clinical laboratory parameters will be summarized across time on study, and the frequency of clinically significant abnormal laboratory values will be tabulated.

Changes in ECG intervals (QT, RR, QTcF, HR, QRS) and vital sign parameters (including systolic and diastolic blood pressure, heart rate, respiration rate, and temperature) will be summarized over time in a similar fashion to laboratory parameters, and any abnormal values will be tabulated. Changes in ECG findings will be presented in data listing format.

Additional safety assessments such as ECGs will be listed by participant.

12.4.7. Interim Analyses

No interim analysis for efficacy will be performed for this study. A DMC will be used to review data periodically throughout the course of this study (see Section 12.6 for further details).

12.4.8. Adjustment for Multiplicity

To control overall type I error, a hierarchical testing procedure will be utilized. Statistical testing will be performed for the analysis of primary and key secondary endpoints in the following order at a 2-sided 0.05 alpha level for each:

1. ORR per RECIST v1.1 at Week 25

2. ORR per TVS at Week 25
3. Mean change from baseline in active ROM at Week 25
4. Mean change from baseline in the PROMIS-Physical Function score at Week 25
5. Mean change from baseline in the Worst Stiffness NRS score at Week 25
6. Mean change from baseline in EQ-VAS at Week 25
7. Proportion of responders based on BPI-30 (Worst Pain) NRS score and narcotic analgesic use at Week 25

12.4.9. Sub-group Analyses

The primary efficacy endpoint and key secondary endpoint(s) will be analyzed in participant subgroups defined as follows:

- Tumor location (lower limb vs all other)
- Region (U.S. vs non-U.S.)
- Participants with disease located in large joints (shoulder, elbow, hip, or knee)
- Participants with disease located in small joints (joints other than the shoulder, elbow, hip, or knee)
- Participants with disease located in the knee
- Participants with PVNS type of TGCT (Localized)
- Participants at sites in the EU region only
- Age
- Gender
- Prior surgery/no surgery
- Prior imatinib/nilotinib vs no prior

12.4.10. Exploratory Efficacy Analyses

Exploratory efficacy analyses of response, TDS, and ROM that are not specified for primary or secondary analyses will be described in the SAP.

Data from tumor response, GP5 (from FACT-G), PGIC, PGIS, CGIC, and CGIS will be summarized by timepoint and treatment group using appropriate continuous or categorical variable summary statistics.

12.4.11. Other Exploratory Analyses

12.4.11.1. Pharmacokinetic Analysis

Plasma concentrations of vimseltinib may be summarized utilizing descriptive statistics. Pharmacokinetics, PK/efficacy and PK/safety may be analyzed and reported separately.

12.4.11.2. Pharmacodynamic Analysis

Biomarkers will be summarized for each timepoint and for change from baseline. Correlation between pharmacodynamic markers and plasma exposure will be explored with descriptive and graphical methods.

Descriptive statistics (mean, standard deviation, median, minimum, maximum, and geometric mean) for each marker will be reported. Graphs of individual values over time according to dose group will be presented.

12.4.11.3. Pharmacogenomics Analysis

Exploratory pharmacogenomics analysis will be described and analyzed separately, if conducted.

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

All available data will be included in data listings.

Unless specified in the individual endpoint analysis, missing data will not be imputed except for the purpose of identification of TEAEs and prior or concomitant medications or procedures with missing start or end time. Algorithms for imputing partial or missing dates will be specified in the SAP.

For the analysis of the response rate, participants who do not have any postbaseline assessment will be considered as nonresponders.

12.6. Data Monitoring Committee

A DMC will monitor the unblinded safety and efficacy data from this study as specified in the DMC charter to help ensure the ongoing safety of study participants. The DMC will consist of an experienced biostatistician and 2 qualified clinicians who are not employees of the Sponsor, with scientific expertise in TGCT and practical experience conducting clinical studies and monitoring safety and efficacy of clinical studies.

13. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

13.1. Quality Control and Quality Assurance

13.1.1. Coordinating Investigator

A Coordinating Investigator is an Investigator assigned the responsibility for the coordination of investigators at different centers participating in a multicenter study.

13.1.2. Study Monitoring

During study conduct, the Sponsor or its agent will conduct periodic monitoring visits to ensure that the protocol and International Conference on Harmonisation (ICH) GCPs are being followed. The monitors will review source documents to confirm that the data recorded on electronic case report forms (eCRFs) are accurate. The Investigator and institution will allow the Sponsor's monitors or designees and appropriate regulatory authorities direct access to source documents to perform this verification.

The study site may be subject to review by the IRB/IEC/REB, and/or to quality assurance audits performed by the Sponsor, or companies working with or on behalf of the Sponsor, and/or to inspection by appropriate regulatory authorities.

It is important that the Investigator and their relevant personnel are available during the monitoring visits and possible audits or inspections and that sufficient time is devoted to the process.

Off-site monitoring may be performed under extraordinary circumstances (eg, COVID-19 pandemic or site policies) that preclude on site monitoring and with approval by the Sponsor. Any off-site monitoring will be performed in accordance with local regulations, where applicable.

13.1.3. Protocol Compliance

The Investigator must conduct the study in compliance with the protocol provided by the Sponsor and given approval/favorable opinion by the IRB/IEC/REB and the appropriate regulatory authorities. Modifications to the protocol must not be made without agreement between both the Investigator and the Sponsor. Changes to the protocol will require written IRB/IEC/REB and the appropriate regulatory authority(ies) approval/favorable opinion prior to implementation, except when the modification is needed to eliminate an immediate hazard(s) to participants. The IRB/IEC/REB may provide, if applicable regulatory authority(ies) permit, expedited review and approval/favorable opinion for minor change(s) in ongoing studies that have the approval/favorable opinion of the IRB/IEC/REB. The Sponsor must ensure that all protocol modifications are submitted to the regulatory authority(ies) in accordance with the governing regulations.

If other unexpected circumstances arise that require deviation from protocol-specified procedures, the Investigator must consult with the Sponsor (and IRB, IEC, or REB, as required) to determine the appropriate course of action.

The site must document all protocol deviations in the participant's source documents. In the event of a significant deviation, the site must notify the Sponsor (and IRB, IEC, or REB, as required). Significant deviations include, but are not limited to, those that involve fraud or misconduct, increase the health risk to the participant, or confound interpretation of primary study assessments.

13.2. Data Handling and Recordkeeping

13.2.1. Electronic Case Report Form

The Sponsor or designee will provide the study sites with secure access to and training on the electronic data capture application sufficient to permit site personnel to enter or correct information in the eCRFs on the participants for which they are responsible.

An eCRF is required and must be completed for each randomized participant. The Investigator has ultimate responsibility for the accuracy, authenticity, and timely collection and reporting of all clinical, safety, and laboratory data entered on the eCRFs and any other data collection forms. Source documentation supporting the eCRF data must indicate the participant's participation in the study and must document the dates and details of study procedures, AEs, other observations, and participant status.

The Investigator, or designated representative, must complete the eCRF as soon as possible after information is collected.

The audit trail will show the user's identification information and the date and time of the any correction. The eCRFs must be signed electronically by the Investigator to attest that the data contained on the eCRFs, including any changes made to the eCRFs, is correct and endorse the final submitted data for the participants for whom the Investigator is responsible.

The completed eCRFs are the sole property of the Sponsor and must not be made available in any form to third parties, except for authorized representatives of the Sponsor or appropriate regulatory authorities, without written permission from the Sponsor.

The Sponsor will retain the eCRF data and corresponding audit trails. A copy of the final archival eCRF will be provided to the site for placement in the Investigator's study file.

13.2.2. Record Retention

To enable evaluations and/or audits from regulatory authorities or the Sponsor, the Investigator agrees to keep records, including the identity of all participating participants (sufficient information to link records, eg, eCRFs and hospital records), all original signed ICFs, eCRFs, SAE forms, source documents, detailed records of treatment disposition, and adequate documentation of relevant correspondence (eg, letters, meeting minutes, telephone calls reports). The records must be retained by the Investigator according to the ICH, local regulations, or as specified in the Clinical Study Agreement, whichever is longer.

If the Investigator becomes unable for any reason to continue to retain study records for the required period (eg, retirement, relocation), the Sponsor must be prospectively notified. The study records must be transferred to a designee acceptable to the Sponsor, such as another Investigator, another institution, or to the Sponsor. The Investigator must obtain the Sponsor's

written permission before disposing of any records, even if retention requirements have been met.

13.3. Ethics

The study will be performed in accordance with the Declaration of Helsinki and are consistent with ICH/GCP and applicable local regulatory requirements.

The Investigator must ensure that this study is conducted in full conformity with Regulations for the Protection of Human Subjects of Research codified in 21 CFR Part 50, 21 CFR Part 54, 21 CFR Part 56, 21CFR Part 312, 21 CFR Part 314 and ICH GCP E6 (R2).

13.3.1. IRB/IEC/REB

It is the responsibility of the Investigator to have prospective approval of the study protocol, protocol amendments, ICF, and other relevant documents, (eg, recruitment advertisements, if applicable) from the IRB/IEC/REB. All correspondence with the IRB/IEC/REB must be retained in the Investigator Site File.

The only circumstance in which an amendment may be initiated prior to IRB/IEC/REB approval is where the change is necessary to eliminate apparent immediate hazards to the participants. In that event, the Investigator must notify the IRB/IEC/REB and the Sponsor in writing immediately after the implementation.

13.3.2. Written Informed Consent

All parties must ensure protection of participant personal data and must not include participant names on any Sponsor forms, reports, publications, or in any other disclosures, except where required by laws. In case of data transfer, the Sponsor must maintain high standards of confidentiality and protection of participant personal data.

The ICF must be in compliance with ICH GCP, local regulatory requirements, and legal requirements.

The ICF used in this study, and any changes made during the course of the study, must be prospectively approved by both the IRB/IEC/REB and the Sponsor before use.

The Investigator must ensure that each study participant is fully informed about the nature and objectives of the study and possible risks associated with participation. The Investigator, or a person designated by the Investigator, must obtain written informed consent from each participant before any study-specific activity is performed. The Investigator must retain the original of each participant's signed consent form.

13.3.3. Participant Confidentiality

The Sponsor and designees affirm and uphold the principle of the participant's right to protection against invasion of privacy. Throughout this study, a participant's source data must only be linked to the Sponsor's clinical study database or documentation via a unique identification number. As permitted by all applicable laws and regulations, limited participant attributes, such as sex, age, or date of birth may be used to verify the participant and accuracy of the participant's unique identification number.

To comply with ICH GCP and to verify compliance with this protocol, the Sponsor requires the Investigator to permit its monitor or designee's monitor, representatives from any regulatory authority (eg, FDA), the Sponsor's designated auditors, and the appropriate IRBs/IECs/REBs to review the participant's original medical records (source data or documents), including, but not limited to, any genetic/genomic data the participant might have from testing done prior to entering the study, laboratory test result reports, ECG reports, admission and discharge summaries for hospital admissions occurring during a participant's study participation, and autopsy reports. Access to a participant's original medical records requires the specific authorization of the participant as part of the informed consent process (Section 13.3.2).

Copies of any participant source documents that are provided to the Sponsor must have certain personally identifiable information removed (ie, participant name, address, and other identifier fields not collected on the participant's eCRF).

13.3.4. Reporting of Safety Issues or Serious Breaches of the Protocol or International Conference on Harmonisation Good Clinical Practice

In the event of any prohibition or restriction imposed (ie, clinical hold) by an applicable Competent Authority, or if the Investigator is aware of any new information which might influence the evaluation of the benefits and risks of the study drug, the Sponsor must be informed immediately.

In addition, the Investigator must inform the Sponsor immediately of any urgent safety measures taken by the Investigator to protect the study participants against any immediate hazard, and of any serious breaches of this protocol or of ICH GCP that comes to the attention of the Investigator.

13.3.5. Liability and Insurance

The Sponsor has subscribed to an insurance policy covering, in its terms and provisions, its legal liability for injuries caused to participating persons and arising out of this research performed strictly in accordance with the scientific protocol as well as with applicable law and professional standards.

14. PUBLICATION POLICY

All scientific, commercial, and technical information disclosed by the Sponsor in this protocol or elsewhere must be considered the confidential and proprietary property of the Sponsor. The Investigator shall hold such information in confidence and shall not disclose the information to any third party except to such of the Investigator's employees and staff as have been made aware that the information is confidential and who are bound to treat it as such and to whom disclosure is necessary to evaluate that information. The Investigator shall not use such information for any purpose other than determining mutual interest in performing the study and, if the parties decide to proceed with the study, for the purpose of conducting the study.

The Investigator understands that the information developed from this clinical study will be used by the Sponsor in connection with the development of the study drug and therefore may be disclosed as required to other clinical investigators, business partners and associates, the FDA, and other government agencies. The Investigator also understands that, to allow for the use of the information derived from the clinical study, the Investigator has the obligation to provide the Sponsor with complete test results and all data developed in the study.

No publication or disclosure of study results will be permitted except under the terms and conditions of a separate written agreement between the Sponsor and the Investigator and/or the Investigator's institution.

15. REFERENCES

Byrne MJ and Nowak AK. Modified RECIST criteria for assessment of response in malignant pleural mesothelioma. Ann Oncol. 2004;15:257-60.

Centers for Disease Control and Prevention. Interpretation of Hepatitis B Serologic Test Results. https://www.cdc.gov/hepatitis/hbv/pdfs/serologicchartv8.pdf. Accessed 10 Nov 2020.

Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (v1.1). Eur J Cancer. 2009;45:228-47.

FACIT.org. Overview. http://www.facit.org/FACITOrg/Overview. Accessed: 06 Oct 2020.

Lacouture ME, Sibaud V, Anadkat MJ, Kaffenberger B, Leventhal J, Guindon K, et al. Dermatologic Adverse Events Associated with Selective Fibroblast Growth Factor Receptor Inhibitors: Overview, Prevention, and Management Guidelines. Oncologist. 2021 Feb;26(2):e316-e326.

National Cancer Institute-Common Terminology Criteria for Adverse Events. https://ctep.cancer.gov/protocoldevelopment/electronic_applications/ctc.htm Accessed: 12 Nov 2020.

Ostergaard M, Edmonds J, McQueen F, Peterfy C, Lassere M, Ejbjerg B, et al. An introduction to the EULAR-OMERACT rheumatoid arthritis MRI reference image atlas. Ann Rheum Dis. 2005 Feb;64(Suppl 1):i3-7.

Ostergaard M, Peterfy CG, Bird P, Gandjbakhch F, Glinatsi D, Eshed I, et al. The OMERACT Rheumatoid Arthritis Magnetic Resonance Imaging (MRI) Scoring System: Updated Recommendations by the OMERACT MRI in Arthritis Working Group. J Rheumatol. 2017 Nov;44(11):1706-12.

Peterfy CG, Guermazi A, Zaim S, Tirman PF, Miaux Y, White D, et al. Whole-Organ Magnetic Resonance Imaging Score (WORMS) of the knee in osteoarthritis. Osteoarthritis Cartilage. 2004 Mar;12(3):177-90.

Plathow C, Klopp M, Thieke C, Herth F, Thomas A, Schmaehl A, et al. Therapy response in malignant pleural mesothelioma – role of MRI using RECIST, modified RECIST and volumetric approaches in comparison with CT. Eur Radiol. 2008;18:1635-43.

Tap WD, Wainberg ZA, Anthony SP, Ibrahim PN, Zhang C, Healey JH, et al. Structure-guided blockade of CSF1R kinase in tenosynovial giant-cell tumor. N Engl J Med. 2015;373:428-37.

Turalio. [Package Insert]. Basking Ridge, NJ: Daiichi Sankyo, Inc.; 2019.

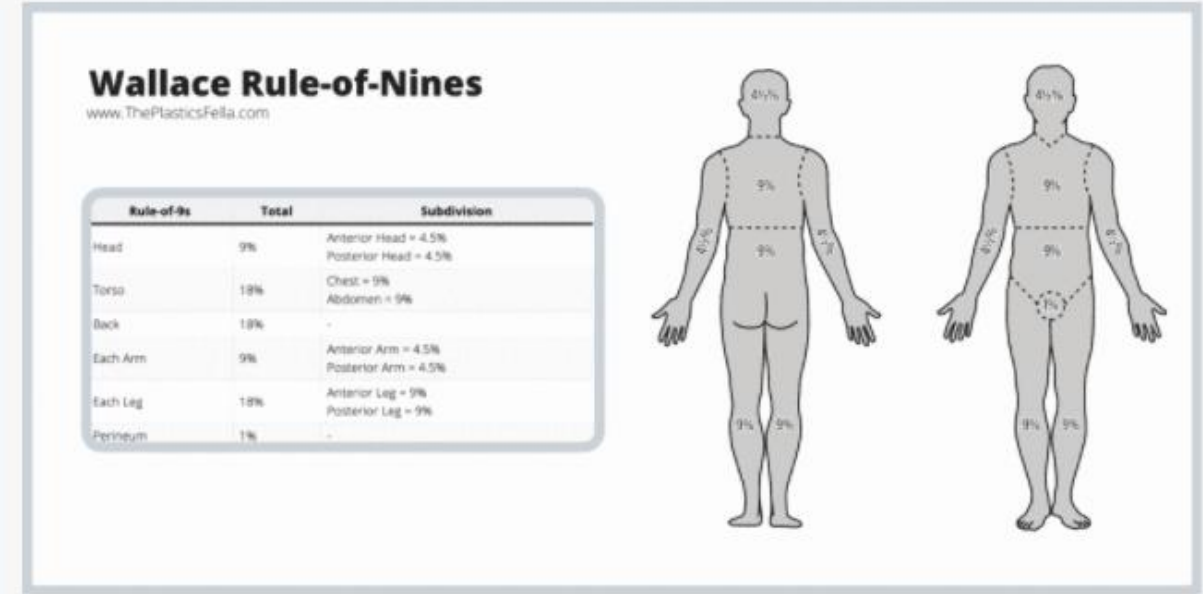
Wallace AB. The exposure treatment of burns. Lancet. 1951;1:501-4.

16. APPENDICES

APPENDIX 1. MEDICATIONS WITH A POSSIBLE OR KNOWN EFFECT ON QT INTERVAL

Refer to the CredibleMeds website (https://crediblemeds.org/) for the most up-to-date list of medications that may or are known to prolong QT interval. Investigative sites are responsible for ensuring that all concomitant medications that a participant receives are administered in accordance with the protocol.

APPENDIX 2. CALCULATING BODY SURFACE AREA "RULE OF 9'S"



Calculating the total body surface area of a burn with Wallace Rule of Nines

Source: https://www.theplasticsfella.com/total-body-surface-area-in-burns/; Wallace, 1951

APPENDIX 3. RESPONSE EVALUATION CRITERIA IN SOLID TUMORS v1.1

Response assessment will be performed according to Response Evaluation Criteria in Solid Tumors, v1.1 (RECIST v1.1) (Eisenhauer et al, 2009) with clarifications/modifications for this protocol described below.

Radiology Evaluation According to RECIST v1.1 - Summary of Response Criteria

Baseline Timepoint Evaluation

- Measurable lesions at baseline are designated as target lesions
  - Target lesions are measured according to the type of lesion. Non-nodal lesions are measured in longest diameter; nodal lesions are measured by short axis.
  - Up to 5 target lesions with no more than 2 lesions per organ are identified at baseline.
  - A Sum of Diameters (SOD) is calculated for target lesions at baseline that includes longest diameters for all non-nodal lesions and the short axis for all nodal lesions.
- Nonmeasurable lesions at baseline are designated as nontarget lesions
- Nontarget lesions are followed qualitatively at baseline.

Follow-up Timepoint Evaluation

- Target lesions
  - Target lesions are re-measured at follow-up and the target lesion SOD is compared to baseline and nadir to determine response/progression status.
  - Decreases in tumor burden must be assessed relative to baseline measurements. Increases in tumor burden are assessed relative to nadir.
- Nontarget lesions
  - Nontarget lesions are followed qualitatively at follow-up timepoints.
- New lesions
  - Unequivocal new lesions are reported at follow-up and are indicative of progressive disease.

Target Lesion Assessment at Follow-up Timepoints

Target Lesions:

- Target lesions are re-measured and no individual lesion assessment is derived.
- A SOD is calculated for target lesions at each follow-up timepoint.
- Lymph nodes that have a short axis <10 mm is considered normal.

- Target lesions selected at baseline should continue to be measured at postbaseline timepoints, regardless of lesion size, unless they are absent. This applies to nodes as well that fall within the normal range with a perpendicular axis <10 mm. As a result, the SOD for a visit may not be 0, but may still qualify for a CR assessment for the current timepoint.

An overall target lesion assessment is derived for the timepoint according to Table 19.

Table 19: Overall Target Lesion Assessment

Category	Definition
Complete Response (CR)	Disappearance of all target lesions. Any pathological lymph nodes must be <10 mm in short axis. Non-nodal targets must be absent.
Partial Response (PR)	≥30% decrease in the SOD of target lesions, taking as reference the baseline sum of diameters.
Stable Disease (SD)	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest SOD while on study.
Progressive Disease (PD)	At least a 20% increase in the SOD 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.
Not Evaluable (NE)	Progression has not been documented and one or more target lesions have not been assessed or have been assessed using a different method than baseline that makes comparability impossible.

Abbreviation: SOD=Sum of Diameters

Nontarget Lesion Assessment at Follow-up Timepoints

- Each nontarget lesion or nontarget lesion group recorded at baseline is reassessed at follow-up and provided with a qualitative assessment. All nontarget lesions should be evaluated visually at each timepoint, and examined for presence or absence and for evidence of unequivocal progression of individual lesions as well as of the overall target lesions.
- **NOTE:** To achieve "unequivocal progression" of nontarget lesions overall, there must be an overall level of substantial worsening in the nontarget disease that is of a magnitude that, even in the presence of SD or PR in target disease, a treating physician would feel it important to change therapy; however, the increase in the size of an individual nontarget lesion alone may not necessarily be classified as PD.

An overall nontarget lesion assessment is derived for the timepoint according to Table 20.

Table 20: Overall Nontarget Lesion Assessment

Category	Definition
Complete Response (CR)	Disappearance of all nontarget lesions. All lymph nodes must be nonpathological in size (<10 mm short axis).
Non-CR/Non-PD	Persistence of one or more nontarget lesion(s)

Category	Definition
Progressive Disease (PD)	Unequivocal progression of existing nontarget lesions
Not Evaluable (NE)	Progression has not been documented and one or more nontarget lesions have not been assessed or have been assessed using a different method than baseline that makes comparability impossible

Reporting New Lesions at Follow-up Timepoints

- New lesions are reported when present and should be unequivocal for new disease.
- The appearance of unequivocal new lesions is consistent with PD regardless of the state of the target lesions.
- There is no minimum size for a new lesion with the exception of new nodal disease. New nodal lesions must be ≥1.0 cm in short axis.
- There are no specific criteria for the identification of new radiographic lesions; however, the finding of a new lesion should be unequivocal (ie, 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 participant's baseline lesions show partial or complete response.
- A lesion identified on a follow-up study in an anatomical location that was not scanned at baseline is considered a new lesion indicative of disease progression.

An overall assessment of new lesions at follow-up timepoints is derived according to Table 21.

Table 21: Overall Assessment by RECIST v1.1 at Follow-up Timepoints

Overall Response at each Assessment Based on Target, Nontarget, and New Lesions			
Target Lesions	**Nontarget Lesions**	**New Lesions**	**Timepoint Response**
CR	CR	No	CR
CR	Non-CR/Non-PD	No	PR
CR	Not all evaluated (NE)	No	PR
PR	Non-PD or not all evaluated (NE)	No	PR
SD	Non-PD or not all evaluated (NE)	No	SD
Not all evaluated	Non-PD or not all evaluated (NE)	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD
None identified at BL	CR	No	CR

Overall Response at each Assessment Based on Target, Nontarget, and New Lesions			
Target Lesions	**Nontarget Lesions**	**New Lesions**	**Timepoint Response**
None identified at BL	Non-CR/Non-PD	No	Non-CR/Non-PD
None identified at BL	Not all evaluated (NE)	No	NE
None identified at BL	PD	Yes or No	PD
None identified at BL	None	No	NE
None identified at BL	None	Yes	PD

Abbreviations: BL=baseline; CR=complete response; NE=not evaluated; PD=progressive disease; PR=partial response; SD=stable disease.

APPENDIX 4. MODIFIED RESPONSE EVALUATION CRITERIA IN SOLID TUMORS

Modified RECIST (mRECIST) criteria is identical to RECIST v1.1, except for:

- Measurements are taken along the short-axis dimension perpendicular to the longest dimension and ideally also to a reproducible adjacent landmark, such as the femoral bone or a tendon

The sum of short-axis dimensions of target lesions (SSD) will be calculated and reported for each timepoint. All other conventions applicable to RECIST v1.1 will apply to mRECIST.

Sources: Byrne and Nowak, 2004; Plathow et al, 2008.

APPENDIX 5. TUMOR VOLUME SCORE

Tumor Volume Score (TVS) is a semi-quantitative MRI scoring system that describes tumor mass and is based on 10% increments of the estimated volume of the maximally distended synovial cavity or tendon sheath involved. A tumor that is equal in volume to that of a maximally distended synovial cavity or tendon sheath was scored 10; a score of 0 indicated no evidence of tumor.

Source: Tap et al, 2015

APPENDIX 6. TISSUE DAMAGE SCORE

Extent and severity of structural damage of affected joints and tendons evident with MRI will be included as exploratory efficacy endpoints and defined as:

- Bone erosion: Based on the RAMRIS-erosion scale originally developed for assessing rheumatoid arthritis of the hands and wrists (Ostergaard et al, 2005; Ostergaard et al, 2017). The scale ranges from 0 to 10 in 10% increments of articular bone eroded and is applied to each of the 14 regions in the knee specified in WORMS (Peterfy et al, 2004) or to each articular bone in the ankle/foot, shoulder, elbow, or wrist. Articular bone is defined as bone within 1 cm of the articular surface.
- Cartilage loss: Based on WORMS in the same regions as bone erosion assessments.
- Bone marrow edema: Based on WORMS in the same regions as bone erosion assessments.
- Joint effusion and popliteal cysts (knee only): Based on WORMS.
- Tendon integrity.

Sources: Ostergaard et al, 2005; Ostergaard et al, 2017; Peterfy et al, 2004.

Signature Page for FINAL 3014-03-001 Amd 3_31May2023

Approval Task	PPD Deciphera Pharmaceuticals, LLC 01-Jun-2023 20:11:44 GMT+0000

Veeva Vault RIM Document ID Number DCC-CLIN-001465