# CLINICAL STUDY PROTOCOL

| | |
|---|---|
| Protocol Number: | PLX108-10 |
| Title: | A Double-blind, Randomized, Placebo-controlled Phase 3 Study of Orally Administered PLX3397 in Subjects with Pigmented Villonodular Synovitis or Giant Cell Tumor of the Tendon Sheath (ENLIVEN) |
| Indication: | Pigmented villonodular synovitis (PVNS) / giant cell tumor of the tendon sheath (GCT-TS) |
| Phase: | 3 |
| Sponsor: | Daiichi Sankyo, Inc.<br>399 Thornall Street<br>Edison, NJ 08837, USA |
| EudraCT Number: | 2014-000148-14 |
| Therapeutic Area: | Antineoplastic agent |
| IND Number: | 117,332 |
| Version: | 9.0, 15 Dec 2017 |
| Superseded Versions: | 8.0, 11 Sep 2017<br>7.0, 10 Feb 2017<br>6.0, 10 Oct 2016<br>5.0, 19 Jul 2016<br>4.0, 25 Mar 2016<br>3.0, 11 Feb 2015<br>2.0, 05 Dec 2014 |
| Original Protocol: | 1.0, 18 Sep 2014 |

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# INVESTIGATOR AGREEMENT

**Sponsor Approval:**

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

| | |
|---|---|
| [redacted] | [redacted] |
| **Print Name** | **Signature** |
| Senior Director, Global Oncology R&D | 15/12/2017 |
| **Title** | **Date (DD MMM YYYY)** |

**Investigator's Signature:**

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

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

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

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

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

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

# TABLE OF CONTENTS

INVESTIGATOR AGREEMENT ..... 2
TABLE OF CONTENTS ..... 3
LIST OF TABLES ..... 10
LIST OF FIGURES ..... 11
GLOBAL AMENDMENT, PROTOCOL V 9.0 ..... 12
LIST OF ABBREVIATIONS ..... 13
PROTOCOL SYNOPSIS ..... 16
1. INTRODUCTION AND BACKGROUND INFORMATION ..... 26
1.1. Scientific Background ..... 26
1.1.1. Pigmented Villonodular Synovitis and Giant Cell Tumors of the Tendon Sheath ..... 26
1.1.2. Pexidartinib (PLX3397) ..... 27
1.2. Nonclinical Studies ..... 27
1.3. Clinical Experience ..... 27
1.3.1. Subjects with PVNS/GCT-TS Treated in Study PLX108-01 ..... 29
1.4. Study Rationale ..... 31
1.4.1. Study Purpose ..... 32
1.5. Risks and Benefits for Study Subjects ..... 32
1.6. Updated Risk Information and Change in Study Conduct ..... 33
2. STUDY OBJECTIVES AND HYPOTHESIS ..... 35
2.1. Study Objectives ..... 35
2.2. Study Endpoints ..... 35
2.2.1. Primary Efficacy Endpoint ..... 35
2.2.2. Secondary Efficacy Endpoints ..... 37
2.2.3. Additional Endpoints ..... 39
2.3. Study Hypothesis ..... 40
3. STUDY DESIGN ..... 41
3.1. Overall Plan ..... 41
3.2. Number of Subjects ..... 45
3.3. Duration of Study ..... 45
4. STUDY POPULATION ..... 46

4.1. Enrollment ....46
4.1.1. Inclusion Criteria ....46
4.1.2. Exclusion Criteria ....47
4.2. Removal of Subject From Therapy ....48
4.2.1. Reasons for Withdrawal/Early Discontinuation ....48
4.2.2. Withdrawal Procedures ....49
4.2.3. Subject Replacement ....49
4.3. Subject Re-screening Procedures ....49
5. TREATMENTS ADMINISTERED ....50
5.1. Investigational Products ....50
5.2. Study Treatment Administration ....50
5.3. Dose Modification Guidelines ....51
5.4. Concomitant Medications ....56
5.5. Precautions and Restrictions ....56
5.6. Blinding and Unblinding ....56
5.6.1. Unblinding ....57
5.6.1.1. Emergency Unblinding ....57
5.6.1.2. Unblinding during Part 1 Week 13 to Week 25 for Disease Progression ....57
5.6.1.3. Unblinding at the End of Part 1 ....58
5.7. Description of Investigational Agents ....58
5.8. Packaging and Labeling ....59
5.9. Storage, Handling, and Accountability ....59
6. STUDY CONDUCT ....61
6.1. Study Personnel and Organizations ....61
6.2. Recruitment of Subjects ....61
6.3. Treatment Group Assignments ....61
6.4. Study Procedures ....61
6.4.1. Demographics and Medical History ....62
6.4.2. Vital Signs and Subject Weight ....62
6.4.3. Physical Examination ....62
6.4.4. Range of Motion Assessment ....62
6.4.5. Electrocardiogram ....62
6.4.6. Echocardiogram ....63

6.4.7. Clinical Laboratory Evaluations ....63
6.4.8. Patient Reported Outcome Instruments ....65
6.4.8.1. Most Disturbing Symptom Assessment ....65
6.4.8.2. BPI Worst Pain NRS Item ....65
6.4.8.3. Worst Stiffness NRS item ....65
6.4.8.4. PROMIS Physical Function Scale ....66
6.4.8.5. EQ-5D-5L ....66
6.4.8.6. Patient Global Impression of Change and Global Rating of Concept Items ....66
6.4.9. Tumor Imaging ....66
6.4.10. Surgical Assessment Questionnaire ....67
6.4.11. Surgical Data and Outcome Follow-up ....67
6.4.12. Analgesic Use and Analgesic Regimen ....68
6.4.13. Healthcare Resource Use and Productivity ....68
6.4.14. Pregnancy Test ....68
6.4.15. Pharmacodynamic Sampling ....68
6.4.16. Pharmacokinetic (PK) Sampling ....69
6.4.17. Adverse Events ....69
6.4.18. Study Treatment Compliance ....70
6.5. Study Procedures ....70
7. STATISTICAL METHODS ....71
7.1. Randomization and Stratification ....71
7.2. Analysis Sets ....71
7.3. Procedures for Handling Missing, Unused, and Spurious Data ....71
7.4. General Statistical Considerations ....72
7.5. Study Population Data ....72
7.6. Efficacy Analyses ....72
7.6.1. Primary Efficacy Analysis ....72
7.6.2. Secondary Efficacy Analyses ....73
7.6.3. Additional Efficacy Analyses ....74
7.6.4. Subgroup Analyses ....76
7.7. Pharmacodynamics/Biomarkers ....76
7.8. Pharmacogenomic Analysis ....77

7.8.1. Genomic or Genetic Banking and Analysis ....77
7.8.1.1. Disclosure of the Results of Genomic or Genetic Analysis ....77
7.8.1.2. Storage and Disposal of Specimens for Genomic or Genetic Banking and Analysis ....77
7.9. Pharmacokinetics and Exposure–Response Analyses ....77
7.10. Safety Analysis ....78
7.10.1. Analysis of Treatment-emergent Adverse Events ....78
7.10.2. Clinical Laboratory Evaluation Analyses ....79
7.10.3. Vital Sign Analyses ....79
7.10.4. Electrocardiogram Analyses ....79
7.10.5. Echocardiogram Analyses ....79
7.10.6. Analysis of Physical Examination Findings ....79
7.10.7. Concomitant Medication Analyses ....80
7.11. Data Monitoring Committee ....80
7.12. Sample Size Determination ....80
8. ETHICAL CONSIDERATIONS ....81
9. SAFETY ASSESSMENT ....82
9.1. Reporting Adverse Events and Serious Adverse Events ....82
9.2. Definitions ....83
9.2.1. Adverse Event ....83
9.2.2. Serious Adverse Event ....83
9.2.3. Adverse Event Severity ....83
9.2.4. Causality Assessment ....84
9.2.5. Action Taken Regarding the Study Treatment ....84
9.2.6. Adverse Event Outcome ....85
9.2.7. Other Action Taken for Event ....85
9.3. Serious Adverse Event Reporting Procedure for Investigators ....85
9.3.1. Reporting by Investigators ....85
9.3.2. Notifying Regulatory Authorities, Investigators, and Institutional Review Boards/Institutional Ethics Committees ....86
9.4. Procedures for Reporting Drug Exposure During Pregnancy and Birth Events ....86
10. STUDY ADMINISTRATIVE INFORMATION ....88

10.1. Study Contacts ....88
10.1.1. Sponsor....88
10.1.2. Medical Monitor....88
10.1.2.1. Sponsor Medical Monitor ....88
10.1.2.2. Contract Research Organization Medical Monitor ....88
10.1.3. SAE Reporting Contact....88
11. ADMINISTRATIVE REQUIREMENTS....89
11.1. Good Clinical Practice ....89
11.2. Data Quality Assurance....89
11.3. Electronic Case Report Form Completion ....89
11.4. Data Management ....89
11.5. Study Monitoring ....90
11.6. Subject Information and Informed Consent ....90
11.7. Subject Confidentiality....90
11.8. Investigator Compliance ....90
11.9. On-site Audits ....91
11.10. Investigator and Site Responsibility for Drug Accountability ....91
11.11. Product Complaints....91
11.12. Study Closure ....91
11.13. Study Documentation and Storage ....92
11.14. Record Retention....93
11.15. Record Keeping....93
12. FINANCING AND INSURANCE ....94
12.1. Finances....94
12.2. Reimbursement, Indemnity, and Insurance....94
13. USE OF INFORMATION ....95
14. REFERENCES....96
15. APPENDICES ....99
15.1. List of Common CYP3A4 Inhibitors and Inducers ....99
15.2. Detailed Study Procedures by Visit — Part 1 ....100
15.2.1. Screening (Day –42 to Day –1)....100
15.2.2. Part 1 – Cycle 1 (Randomization)....101
15.2.3. Part 1–Cycle 1, Day 1 (P1-C1D1; Week 1) ....101

15.2.4. Part 1–Cycle 1, Day 8 (P1-C1D8; Week 2) ± 2 days....103
15.2.5. Part 1–Cycle 1, Day 15 (P1-C1D15; Week 3) ± 2 days....103
15.2.6. Part 1–Cycle 1, Day 22 (P1-C1D22; Week 4) ± 2 days....103
15.2.7. Part 1–Cycle 2, Day 1 (P1-C2D1; Week 5) ± 2 days....104
15.2.8. Part 1–Cycle 2, Day 8 (P1-C2D8; Week 6) ± 2 days....104
15.2.9. Part 1–Cycle 2, Day 15 (P1-C2D15; Week 7) ± 2 days....104
15.2.10. Part 1–Cycle 2, Day 22 (P1-C2D22; Week 8) ± 2 days....104
15.2.11. Part 1–Cycle 3, Day 1 (P1-C3D1; Week 9) ± 7 days....104
15.2.12. Part 1–Cycle 3, Day 15 (P1-C3D15; Week 11) ± 7 days....105
15.2.13. Part 1–Cycle 4, Day 1 (P1-C4D1; Week 13) ± 7 days....105
15.2.14. Part 1–Cycle 5, Day 1 (P1-C5D1; Week 17) ± 7 days....106
15.2.15. Part 1–Cycle 6, Day 1 (P1-C5D1; Week 21) ± 7 days....106
15.2.16. Part 1 Completion visit/Early Termination Visit (Week 25) ± 7 days....107
15.2.17. Part 1 28 Day Post-Treatment Visit (last dose + 28 days) ± 7 days....108
15.2.18. Part 1 End-of-Study/12 Week Post-Treatment Visit (12 weeks ± 7 days after the last dose)....109
15.3. Detailed Study Procedures by Visit — Part 2....110
15.3.1. Part 2–Cycle 1, Day 1 (P2-C1D1; Week 25)....110
15.3.2. Part 2–Cycle 1, Day 8 (P2-C1D8; Week 26) ± 2 days....111
15.3.3. Part 2–Cycle 1, Day 15 (P2-C1D15; Week 27) ± 2 days....111
15.3.4. Part 2–Cycle 1, Day 22 (P2-C1D22; Week 28) ± 2 days....112
15.3.5. Part 2–Cycle 2, Day 1 (P2-C2D1; Week 29) ± 2 days....112
15.3.6. Part 2–Cycle 2, Day 8 (P2-C2D8; Week 30) ± 2 days....113
15.3.7. Part 2–Cycle 2, Day 15 (P2-C2D15; Week 31) ± 2 days....113
15.3.8. Part 2–Cycle 2, Day 22 (P2-C2D22; Week 32) ± 2 days....113
15.3.9. Part 2–Cycle 3, Day 1 (P2-C3D1; Week 33) ± 7 days....113
15.3.10. Part 2–Cycle 3, Day 15 (P2-C3D15; Week 35) ± 7 days....113
15.3.11. Part 2–Cycle 4, Day 1 (P2-C4D1; Week 37) ± 7 days....113
15.3.12. Part 2–Cycle 5, Day 1 (P2-C5D1; Week 41) ± 7 days....114
15.3.13. Part 2–Cycle 6, Day 1 (P2-C6D1; Week 45) ± 7 days....115
15.3.14. Part 2–Cycle 7, Day 1 (P2-C7D1; Week 49) ± 7 days....115
15.3.15. Part 2–Cycle 10+, Day 1 (P2-C10+D1; Week 61+) ± 7 days....116
15.3.16. Post-Treatment Visit (Part 2)....117

15.3.17. End-of-Study or Early Termination Visit ....118
15.4. Detailed Study Procedures by Visit — Surgical Outcome ....119
15.4.1. Four weeks Prior to Surgery ....119
15.4.2. During or shortly after Surgery ....119
15.4.3. 4 Months (± 2 weeks) after Surgery ....119
15.4.4. 8, 12, 18, and 24 Months (± 2 weeks) after Surgery ....120
15.5. Brief Pain Inventory (BPI) Worst Pain Numeric Rating Scale (NRS) Item ....120
15.6. Worst Stiffness NRS item ....120
15.7. PROMIS Physical Function Scale ....121
15.8. EQ-5D-5L ....124
15.9. Patient Global Impression of Change and Rating of Concept Items ....127
15.10. Surgical Assessment Questionnaire ....128
15.11. Employment status and productivity questions ....128
15.12. Healthcare Resource Use Questions ....130
15.13. Schedule of Events ....132

# LIST OF TABLES

Table 2.1: Definitions of Response for the Primary Efficacy Endpoint ....36
Table 5.1: Dose Modification Guidelines for Treatment-related Toxicities....52
Table 5.2: Dose Modification Guidelines for Liver Function Abnormalities ....54
Table 5.3: Additional Liver Evaluation ....55
Table 6.1: PK Schedules ....69
Table 15.1: Sample Surgical Assessment Questionnaire....128
Table 15.2: Schedule of Events – Part 1 (Blinded, Placebo-controlled Phase) ....133
Table 15.3: Schedule of Events – Part 2 (Open-label Phase) ....139
Table 15.4: Schedule of Events – For Subjects Who Undergo Surgical Resection ....143

# LIST OF FIGURES

Figure 3.1: Study Schematic* ..... 42

Figure 3.2: Post-treatment Assessments Vary With Reason for Study Withdrawal* ..... 44

# GLOBAL AMENDMENT, PROTOCOL V 9.0

**Amendment Rationale:**

The main purpose of this amendment is to update the safety information for pexidartinib and to revise the dose modification criteria as requested by the US FDA. No changes are made to eligibility criteria, because enrollment has been completed for this study.

**Changes to the Protocol:**

Please refer to the comparison document for protocol version 8.0 (dated 11 September 2017) vs. protocol version 9.0 (dated 15 December 2017) for actual changes in-text. The summary of changes below is a top-line summary of major changes in the PLX108-10 clinical study protocol (Version 9.0) by section.

| **DESCRIPTION OF EACH HIGH-LEVEL CHANGE** | |
|---|---|
| 1 | **The safety data for pexidartinib were updated.**<br>The following sections of the protocol were updated:<br>• Section 1.6 (Updated Risk Information and Change in Study Conduct) |
| 2 | **The criteria for pexidartinib dose modification were revised.**<br>The following sections of the protocol were updated:<br>• Section 5.3 (Dose Modification Guidelines)<br>• Section 15.13 (Schedule of Events) |

# LIST OF ABBREVIATIONS

| Abbreviation or Term | Definition/Explanation |
|---|---|
| AE | Adverse event |
| ALT | Alanine aminotransferase |
| AML | Acute myeloid leukemia |
| AST | Aspartate aminotransferase |
| $AUC_{ss}$ | Area under the time–concentration curve at steady state |
| BPI | Brief Pain Inventory |
| $C_{av}$ | Average concentration |
| CI | Confidence Interval |
| $C_{max}$ | Peak concentration |
| CR | Complete response |
| CSF-1 | Colony stimulating factor 1 |
| CSF1R | Receptor for Colony stimulating factor 1 |
| CTCAE | Common Toxicity Criteria for Adverse Events |
| $C_{trough}$ | Minimum concentration |
| CVA | Cerebrovascular accident |
| CYP | Cytochrome P450 |
| DMC | Data Monitoring Committee |
| DSI | Daiichi Sankyo, Inc. |
| ECG | Electrocardiogram |
| ECHO | Echocardiogram |
| eCRF | Electronic case report form |
| EDC | Electronic data capture |
| EIU | Exposure in utero |
| EQ-5D-5L | EuroQol five-dimensional descriptive system |
| EU | European Union |
| Flt3 | fms-like tyrosine kinase 3 |
| FSH | Follicle-stimulating hormone |
| GCP | Good Clinical Practice |
| GCT-TS | Giant cell tumor of the tendon sheath |
| GGT | Gamma-glutamyl transpeptidase |

| Abbreviation or Term | Definition/Explanation |
|---|---|
| HCl | Hydrochloride |
| HCRU | Healthcare resource use |
| HCV | Hepatitis C virus |
| IB | Investigator's Brochure |
| ICH | International Conference on Harmonisation |
| IEC | Independent ethics committee |
| INR | International normalized ratio |
| IRB | Institutional review board |
| ITT | Intent-to-Treat |
| LH | Luteinizing hormone |
| MedDRA | Medical Dictionary for Drug Regulatory Activities |
| Mg | Milligram |
| MMRM | Mixed models for repeated measurements |
| MRI | Magnetic resonance imaging; magnetic resonance image |
| MUGA | Multi-gated acquisition |
| NCI | National Cancer Institute |
| NOAEL | No Observed Adverse Effect Level |
| NRS | Numeric rating scale |
| OTC | Over-the-counter |
| PD | Progressive disease |
| PDy | Pharmacodynamic(s) |
| PGx | Pharmacogenomic |
| PK | Pharmacokinetic(s) |
| PopPK | Pooled population pharmacokinetic |
| PR | Partial response |
| PRO | Patient-reported outcome |
| PROMIS | Patient-reported Outcomes Measurement Information System |
| PT | Preferred term |
| PVNS | Pigmented villonodular synovitis |
| QD | Once daily |
| QTc | Corrected QT interval |
| QTcF | Fridericia corrected QT interval |

| Abbreviation or Term | Definition/Explanation |
|---|---|
| RAMRIS | Rheumatoid Arthritis MRI Score |
| RECIST | Response Evaluation Criteria in Solid Tumors |
| RNA | Ribonucleic acid |
| ROM | Range of motion |
| SAE | Serious adverse event |
| SAP | Statistical Analysis Plan |
| SAVER | Serious adverse event report |
| SD | Stable disease |
| SOC | System organ class |
| SSD | Sum of the short-axis dimension |
| SUSAR | Suspected unexpected serious adverse reaction |
| TEAE | Treatment-emergent adverse event |
| TGCT | Tenosynovial giant cell tumor |
| TVS | Tumor Volume Score |
| ULN | Upper limit of normal |
| US | United States |
| WORMS | Whole Organ MRI Score |

# PROTOCOL SYNOPSIS

| | | | | | |
|---|---|---|---|---|---|
| **EudraCT No.** | 2014-000148-14 | **IND No.** | 117,332 | **Protocol No.** | PLX108-10 |
| **Investigational Product** | Pexidartinib (PLX3397) | | **Active Ingredient(s) INN** | | Pexidartinib (PLX3397) |
| **Study Title** | A Double-blind, Randomized, Placebo-controlled Phase 3 Study of Orally Administered PLX3397 in Subjects With Pigmented Villonodular Synovitis or Giant Cell Tumor of the Tendon Sheath (ENLIVEN) | | | | |
| **Study Phase** | 3 | | | | |
| **Indication Under Investigation** | Pigmented villonodular synovitis (PVNS) / giant cell tumor of the tendon sheath (GCT-TS), also known as tenosynovial giant cell tumors (TGCT), localized and diffuse types, according to the 2013 World Health Organization classification system. | | | | |
| **Study Objectives** | The primary objective of this study is to compare the response rate of pexidartinib with that of placebo per Response Evaluation Criteria in Solid Tumors, version 1.1 (RECIST 1.1) at Week 25 in subjects with symptomatic, locally advanced PVNS or GCT-TS.<br>The secondary efficacy objectives are to evaluate: (i) patient-reported outcomes (PROs), including the Brief Pain Inventory (BPI) Worst Pain Numeric Rating Scale (NRS) item, Patient-reported Outcomes Measurement Information System (PROMIS) Physical Function Scale, and Worst Stiffness NRS item, at Week 25; (ii) response based on Tumor Volume Score (TVS) at Week 25; (iii) range of motion (ROM) at Week 25; and (iv) duration of response.<br>Other objectives are to evaluate: (i) other measures of efficacy, (ii) long-term safety, (iii) pharmacokinetics (PK), and (iv) pharmacodynamics (PDy) of pexidartinib in treated subjects. | | | | |
| **Study Design** | This trial is a two-part multi-center Phase 3 study in subjects with symptomatic PVNS or GCT-TS for whom surgical resection would be associated with potentially worsening functional limitation or severe morbidity (locally advanced disease). In Part 1, the double-blind phase, eligible candidates will be centrally randomized in a 1:1 ratio to receive either pexidartinib or placebo for 24 weeks. Randomization will be stratified by US versus non-US sites and by upper extremity vs. lower extremity involvement.<br>Subjects will take five capsules a day (1000 mg/d pexidartinib or | | | | |

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| | matching placebo) divided into a morning dose of two capsules and an evening dose of three capsules for the first 2 weeks in Part 1. Thereafter, the dose will be reduced to four capsules a day (800 mg/d pexidartinib or matching placebo) divided equally between the morning and evening doses. Doses will be taken in the fasting state at approximately the same times of the day and approximately 12 hours apart. Each treatment cycle is 28 days and subjects will be treated for up to 6 Cycles. Dose reductions, interruptions, and re-escalations after previous reductions for toxicity are permitted according to pre-specified guidelines. Those subjects, whether on pexidartinib or matching placebo, who complete Part 1 (ie, complete 24 weeks of dosing and the Week 25 assessments) will be eligible to advance to Part 2, a long-term treatment phase where all subjects will receive open-label pexidartinib at a maximum starting dose of four capsules a day (800 mg/d pexidartinib). Effective 30 Sep 2016, per study Data Monitoring Committee (DMC) recommendation, subjects on placebo are no longer allowed into Part 2 to receive open-label pexidartinib.<br><br>MRIs will be performed at Week 13 (Cycle 4, Day 1 visit of Part 1) and Week 25. For those subjects who undergo surgical resection, an MRI will be performed 4 months after surgery. All MRI scans will be assessed by central readers blinded to treatment assignment and other clinical study data during both Parts 1 and 2 of the study, according to procedures outlined in a separate MRI Imaging Charter. The central MRI assessment report of progression status will not be provided unless the Investigator requests an expedited central review of a scan.<br><br>If disease progression is indicated clinically or by local radiologic assessment according to RECIST 1.1 at or after Week 13 but before Week 25, the Investigator may request a central review for evaluation of disease progression. If a central reading confirms RECIST 1.1-defined disease progression, treatment assignment will be unblinded, and subjects receiving placebo will be eligible for early entry into Part 2 of the study. Effective 30 Sep 2016, subjects receiving placebo will be discontinued instead of being eligible to enter Part 2. Subjects receiving pexidartinib will be discontinued from the study unless the Investigator and the Sponsor's Medical Monitor judge that the subject would potentially benefit from continued treatment with pexidartinib. During Parts 1 & 2 of the protocol, the Investigator may request an expedited central review of a scan locally assessed as disease progression according to RECIST 1.1.<br><br>All subjects in Part 2 will continue to receive open-label pexidartinib until all subjects have either reached at least the Week 49 visit (ie, an additional 24 weeks of open-label pexidartinib treatment beyond the placebo-controlled phase) or withdrawn from the trial. Those subjects who complete Part 2 will be eligible to continue for longer efficacy and |

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| | safety follow-up or to enter a separate protocol to continue receiving pexidartinib.<br><br>For statistical analysis of endpoints at the end of Part 1, a clinical data cut-off date will be defined for the point when all randomized subjects complete or are discontinued from Part 1 with appropriate End of Part 1 follow-up. All data up to this date will be cleaned. Unblinding of database will be performed to facilitate the data analyses, including the data from the double-blind Part 1 and available data from Part 2. Such unblinding is only intended for the sponsor and the Contract Research Organization. Subjects who entered Part 2 may continue to receive open-label pexidartinib treatment. Updated analysis of Part 2 data only, in the form of summary and descriptive statistics, will be performed at the end of the trial. Additional updates between the above-mentioned cut-off and end of the trial may also be performed.<br><br>A range-of-motion assessment in the affected joint or tumor location will be performed by an independent and blinded third party assessor at specified time points. PRO instruments will also be completed at specified time points.<br><br>Ongoing safety will be monitored by an independent DMC according to a separate charter.<br><br>Subjects who end their study participation early with no radiologic disease progression will undergo: (i) the 28 Day Post-treatment Visit assessment *with* an MRI 28 ± 7 days after their last dose of study treatment; and (ii) a final MRI 12 weeks ± 7 days after their last dose of study treatment or before any new PVNS therapy, including surgery, whichever occurs first (the "Part 1 End-of-Study/12 Week Post-Treatment Visit"). After completion of the end of Part 1 assessments (Part 1 Completion visit/Early Termination visit), subjects who wish to continue onto the open label part of this study (Part 2) will be unblinded and those on placebo will be discontinued; subjects on pexidartinib in Part 1 may continue into Part 2 to continue to receive pexidartinib. Subjects who complete Part 2 and choose to enter a separate protocol to continue receiving pexidartinib will not have the Post-treatment and End-of-Study Visit assessments. Subjects who terminate the study with radiologic disease progression will undergo the Post-treatment Visit assessment *without* an MRI 28 ± 7 days after their last dose of study treatment or before any new PVNS therapy, including surgery, whichever occurs first.<br><br>Subjects are allowed to undergo surgical resection of their tumor after the completion of Part 1. For subjects who undergo surgical resection within 12 weeks after their last dose of study treatment, they will not have the End-of-Study Visit assessments but will follow a separate visit schedule after the decision of surgery is made. The surgery is recommended to be performed 1-3 weeks after the last dose of study |

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| | treatment. Details of the surgery and its short and long term outcome will be collected. Data collection for the surgery and its outcome may continue in a separate protocol. |
| **Inclusion Criteria** | 1. Age ≥ 18 years.<br>2. A diagnosis of PVNS or GCT-TS (i) that has been histologically confirmed either by a pathologist at the treating institution or a central pathologist, and (ii) where surgical resection would be associated with potentially worsening functional limitation or severe morbidity (locally advanced disease), with morbidity determined consensually by qualified personnel (eg, two surgeons or a multi-disciplinary tumor board).<br>3. Measurable disease as defined by RECIST 1.1 (except that a minimal size of 2 cm is required), assessed from MRI scans by a central radiologist.<br>4. Symptomatic disease because of active PVNS or GCT-TS, defined as one or more of the following:<br>a. a worst pain of at least 4 at any time during the week preceding the Screening Visit (based on scale of 0 to 10, with 10 representing "pain as bad as you can imagine").<br>b. a worst stiffness of at least 4 at any time during the week preceding the Screening Visit (based on a scale of 0 to 10, with 10 representing "stiffness as bad as you can imagine").<br>5. Stable prescription of analgesic regimen during the 2 weeks prior to randomization.<br>6. During the 2 weeks prior to randomization, at least 4 of 7 consecutive days of BPI Worst Pain NRS items and Worst Stiffness NRS items completed correctly.<br>7. Women of childbearing potential must have a negative serum pregnancy test within the14-day period prior to randomization. (Where demanded by local regulations, this test may be required within 72 hours of randomization.)<br>8. Males and females of childbearing potential are permitted in the study so long as they consent to avoid getting their partner pregnant or becoming pregnant, respectively, by using a highly effective contraception method, as described below, throughout the study and for up to 90 days after completion. Highly effective methods of contraception include: intra-uterine device (nonhormonal or hormonal), bilateral tubal occlusion, vasectomy, sexual abstinence, or barrier methods (e.g., condom, diaphragm) used in combination with hormonal methods associated with inhibition of ovulation. Women of non-childbearing potential may be included if they are either surgically sterile or have been |

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| | postmenopausal for ≥ 1 year. Women who have documentation of at least 12 months of spontaneous amenorrhea and have an follicle-stimulating hormone level > 40 mIU/mL will be considered postmenopausal.<br>9. Adequate hematologic, hepatic, and renal function, defined by:<br>• Absolute neutrophil count ≥ 1.5× $10^9$/L<br>• Hemoglobin > 10 g/dL<br>• Platelet count ≥ 100 × $10^9$ /L<br>• AST/ALT ≤ 1.5× ULN<br>• Total bilirubin ≤ 1.5× ULN<br>• Serum creatinine ≤ 1.5× ULN<br>10. Willingness and ability to complete the BPI Worst Pain NRS item, Worst Stiffness NRS item, PROMIS Physical Function Scale, and other self-assessment instruments throughout the study.<br>11. Willingness and ability to use an electronic diary.<br>12. Willingness and ability to provide written informed consent prior to any study-related procedures and to comply with all study requirements. |
| **Exclusion Criteria** | 1. Investigational drug use within 28 days of randomization.<br>2. Previous use of pexidartinib or any biologic treatment targeting colony stimulating factor 1 (CSF-1) or the CSF-1 receptor; previous use of oral tyrosine kinase inhibitors, eg, imatinib or nilotinib, are allowed.<br>3. Active cancer (either concurrent or within the last year of starting study treatment) that requires therapy (eg, surgical, chemotherapy, or radiation therapy), with the exception of adequately treated basal or squamous cell carcinoma of the skin, melanoma in-situ, carcinoma in-situ of the cervix or breast, or prostate carcinoma with a prostate-specific antigen value <0.2 ng/mL.<br>4. Known metastatic PVNS/GCT-TS.<br>5. Active or chronic infection with hepatitis C virus or hepatitis B virus or known active or chronic infection with human immunodeficiency virus.<br>6. Known active tuberculosis.<br>7. Significant concomitant arthropathy in the affected joint, serious illness, uncontrolled infection, or a medical or psychiatric history |

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| | that, in the Investigator's opinion, would likely interfere with a candidate's study participation or the interpretation of his or her results.<br>8. Women who are breastfeeding.<br>9. A screening Fridericia corrected QT interval (QTcF) ≥ 450 ms (men) or ≥ 470 ms (women).<br>10. MRI contraindications.<br>11. History of hypersensitivity to any excipients in the investigational product.<br>12. Inability to swallow capsules. |
| **Study Duration** | Each subject will spend a maximum of 6 weeks in screening. Part 1 will be a maximum of 24 weeks in duration. Patients for whom disease progression is confirmed at or after Week 13 but before Week 25 (by independent central radiological evaluation) and are taking placebo are eligible for entry into Part 2 early prior to 30 Sep 2016. The duration of Part 2 will vary among subjects, as this portion of the trial will continue until all subjects in this phase have either completed at least the Week 49 Visit or withdrawn from the study. The study will end with the last subject last visit. Subjects who complete Part 2 will be eligible to continue for longer efficacy and safety follow-up or to enter a separate protocol to continue receiving pexidartinib until disease progression, unacceptable toxicity, or the occurrence of other termination criteria. |
| **Study Sites & Locations** | Approximately 45 study sites internationally across the US, Canada, EU, and Australia. |
| **Planned Sample Size** | Approximately 126 subjects across sites globally are planned. |
| **Test Product, Dose, and Route of Administration** | The study treatment, either pexidartinib or placebo, will be administered orally daily in capsule form. Each capsule of pexidartinib will contain 200 mg of PLX3397 (J-3397-AF in hydroxypropyl methylcellulose capsules) or matching placebo. In Part 1, subjects will take five capsules a day (1000 mg/d pexidartinib or matching placebo) divided into a morning dose of two capsules and an evening dose of three capsules. After 2 weeks (P1-C1D15), dosing will be reduced to two capsules in the morning and two capsules in the evening (800 mg/d pexidartinib or matching placebo). All subjects will begin Part 2 by continuing to take the same number of capsules per day of open-label 800 mg/d pexidartinib. Doses will be taken in the fasting state (no food for 1 hour before and 2 hours after dosing, with a low-fat snack if needed) at approximately the same times of the day and approximately 12 hours apart. Each treatment cycle is 28 days. |

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| | The study treatment for home administration during Part 1 will be dispensed to the subject for the first time at the Cycle 1, Day 1 visit of Part 1, and the study treatment for home administration during Part 2 will be dispensed to the subject for the first time at the Cycle 1, Day 1 visit of Part 2. |
| **Dose Modification Guidelines** | Reduction or interruption of dosing can be implemented at any time to manage intolerable or clinically significant toxicity. Subjects unable to tolerate two capsules per day (400 mg/d pexidartinib or matching placebo) will be discontinued. Guidelines for dose modification are specified in Section 5.3. |
| **Study Assessments** | *Efficacy* — MRI, range of motion, BPI Worst Pain NRS item, Worst Stiffness NRS item, PROMIS Physical Function Scale, EuroQol five-dimensional descriptive system (EQ-5D-5L), Surgical Assessment Questionnaire, major healthcare resource use (HCRU) and productivity, analgesic medications.<br><br>*Safety* — Physical examination, vital signs, 12-lead electrocardiogram (ECG), echocardiography, adverse event reports, serum chemistry, hematology, coagulation tests, urinalysis, hormone testing (as applicable), concomitant medications.<br><br>*PK* — PK blood samples will be drawn.<br><br>*PDy* — Plasma samples for pexidartinib PDy markers and for exploratory markers of monocyte or macrophage activities. Available archival surgical tissue from tumors will be collected and stored for exploratory purposes. |
| **Efficacy Endpoints** | Primary efficacy endpoint:<br><br>The proportion of subjects who achieve a complete response (CR) or partial response (PR) at the Week 25 visit based on centrally read MRI scans and RECIST 1.1. |
| | Secondary efficacy endpoints:<br><br>• Mean change from baseline in range of motion of the affected joint, relative to a reference standard for the same joint, at the Week 25 visit<br>• Proportion of responders based on centrally evaluated MRI scans and TVS at the Week 25 visit<br>• Mean change from baseline score in the PROMIS Physical Function Scale at the Week 25 visit<br>• Mean change from baseline score in the Worst Stiffness NRS item at the Week 25 visit |

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| | • Proportion of responders based on the BPI Worst Pain NRS item and analgesic use by BPI-30 definition [subject who (i) experienced a decrease of at least 30% in the mean BPI Worst Pain NRS item and (ii) did not experience a 30% or greater increase in narcotic analgesic use compared to baseline]<br>• Duration of response (CR or PR) based on MRI and RECIST 1.1<br>• Duration of response (CR or PR) based on MRI and TVS |
| | Additional efficacy endpoints to be analyzed at Week 25, with the exception of duration endpoints or otherwise indicated, include:<br>• Proportion of responders on the BPI Worst Pain NRS item and analgesic use by BPI-2p definition [subject who (i) experienced a decrease of at least 2 points in the mean BPI Worst Pain NRS item and (ii) did not experience a 30% or greater increase in narcotic analgesic use compared to baseline]<br>• Proportion of responders on the BPI Worst Pain NRS item and analgesic use by BPI-50 definition [subject who (i) experienced a decrease of at least 50% in the mean BPI Worst Pain NRS item and (ii) did not experience a 30 % or greater increase in narcotic analgesic use compared to baseline]<br>• Proportion of responders on the Worst Stiffness NRS item<br>• Proportion of responders on the PROMIS Physical Function Scale<br>• Mean change from baseline in the BPI Worst Pain NRS item<br>• Patient Global Impression of Change item for tumor-related stiffness and Patient Global Rating of Concept item for ability to carry out every day physical activities.<br>• Duration of BPI-based symptom response, analyzed for BPI-30, BPI-50 and BPI-2p.<br>• Results of the Surgical Assessment Questionnaire in Part 1.<br>• Response based on the change in the sum of the short-axis dimension (SSD) of the tumor on MRI, referred to as "modified RECIST 1.1-SSD"<br>• Amount of joint/tissue damage (eg, bone erosion, bone edema, cartilage loss) assessed on MRI based on adaptations of the Rheumatoid Arthritis MRI Score and Whole Organ MRI Score<br>• Analgesic use expressed as morphine-equivalent doses in Part |

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| | 1<br>• EQ-5D-5L parameters in Part 1<br>• Major HCRU and productivity in Part 1<br>• Duration of response based on MRI and modified RECIST 1.1-SSD<br>• Response based on the most disturbing symptom of pain, stiffness, or compromised ability to carry out everyday activities<br>• Proportion of subjects receiving surgical resection of their tumor by 25 weeks, 49 weeks, 73 weeks, and 97 weeks of pexidartinib treatment |
| **PK Analysis** | Plasma–concentration time data for pexidartinib will be summarized by visit and time using descriptive statistics. The data from these samples will be analyzed using a pooled population pharmacokinetic (PopPK) approach using nonlinear mixed effects modeling. PK parameters will include apparent clearance and volume of distribution along with transfer rate constants such as absorption and elimination rates. Additionally, based on post-hoc Bayesian methods, estimates of exposure such as $C_{max}$, $C_{trough}$, $C_{av}$ and $AUC_{ss}$ may also be reported |
| **PDy/Biomarker Analysis** | No formal statistical analysis of PDy endpoints will be performed. PDy data from each assay will be listed and possible relationships between PK and PDy variables may be explored. Any biological activity will be described. |
| **Statistical Analyses** | Efficacy analyses will be performed on the intent-to-treat (ITT) Analysis Set. For the efficacy analyses, subjects will be included in the treatment group to which they were randomized.<br>The primary endpoint is the proportion of subjects who achieve a CR or PR at the Week 25 Visit based on centrally read MRI scans and RECIST 1.1. The proportions in the two treatment groups will be compared using Fisher's exact test (two-sided) at the alpha = 0.05 level of significance. In addition, the two-sided 95% confidence interval (CI) for the difference between the responder proportions in the two treatment groups will be provided using the Wilson method.<br>The following treatment comparisons at the Week 25 visit are secondary efficacy analyses:<br>1. Mean change from baseline in range of motion of the affected joint, relative to a reference standard for the same joint;<br>2. Proportion of responders based on centrally evaluated MRI scans and TVS; |

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| | 3. Mean change from baseline in the PROMIS Physical Function Scale;<br>4. Mean change from baseline in the Worst Stiffness NRS item;<br>5. Proportion of responders by BPI Worst Pain NRS item and analgesic use by BPI-30 definition.<br><br>These above-listed endpoints will be analyzed using a hierarchical ("gatekeeping") testing procedure. Thus, if the primary analysis is statistically significant ($p<0.05$), then secondary endpoint #1 will be analyzed, also based on the use of a two-sided test at the alpha=0.05 level of significance. If secondary endpoint #1 is statistically significant ($p<0.05$), then the testing procedure will proceed to secondary endpoint #2, and so on. If the test for a particular endpoint is not statistically significant, the inference for all subsequent endpoints in the hierarchy will not be performed.<br><br>Duration of response will also be a secondary efficacy endpoint and will be summarized by treatment group using the Kaplan-Meier product limit approach. The estimate and 95% CI will be provided for the median and the $25^{th}$ and $75^{th}$ percentiles.<br><br>All secondary endpoints of mean changes at Week 25 will be analyzed using mixed models for repeated measurements. The dependent variable will be the change from baseline. Each of these models will include fixed effects for treatment group, time point, treatment group-by-time interaction, stratification factor of US sites versus non-US sites, and the baseline value of the corresponding endpoint as well as the baseline-by-time interaction. An unstructured variance-covariance matrix will be used. Statistical comparisons between groups will be made at the specified time point. For secondary endpoints #2 and #5, the proportions of responders in the two treatment groups will be compared using Fisher's exact test.<br><br>Safety analyses will be performed on the Safety Analysis Set, and safety variables, including treatment-emergent adverse events, laboratory tests, vital signs, and ECGs, will be summarized.<br><br>*Sample Size Evaluation* — The assumed responder rates for the primary endpoint are 10% (placebo) and 35% (pexidartinib). Based on the use of a two-sided, two-sample comparison of proportions at the alpha=0.05 level of significance by Fisher's exact test, a sample size of 126 ITT subjects (63 per arm) provides 90% power to detect this magnitude of difference. |

# 1. INTRODUCTION AND BACKGROUND INFORMATION

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

## 1.1. Scientific Background

### 1.1.1. Pigmented Villonodular Synovitis and Giant Cell Tumors of the Tendon Sheath

Pigmented villonodular synovitis (PVNS) and giant cell tumors of the tendon sheath (GCT-TS) are members of a single condition referred to as "tenosynovial giant cell tumour (TGCT), localized and diffuse type" and have a common pathogenesis [1]. They are rare proliferative neoplasms involving the synovium and tendon sheaths that typically present in young and middle-aged adults of both sexes. PVNS and GCT-TS are usually monoarticular processes that involve the bone, soft tissue, synovium, or tendon sheath of small or large joints. Symptoms initially may be minimal due to the slowly progressive nature of the disease, but as the tumor mass grows and gradually expands within the fixed confines of the intra-articular space (and surrounding tissue); symptoms such as pain, stiffness, swelling, and limitation in range of motion (ROM) can become severe and result in marked functional limitation. The diagnosis of PVNS is definitively made from pathologic evaluation; however, features highly suggestive of the disease may be found on radiologic imaging, including computed tomography and magnetic resonance imaging (MRI).

PVNS and GCT-TS tumors predominantly consist of mononuclear and multinucleated giant cells. In both diseases, expansion of the tumor mass appears to be driven by the presence of abundant Colony stimulating factor 1 (CSF-1) expressed by a subset of cells within the tumor and often associated with genetic translocations linking the collagen 6A3 gene (on 2q35) with the CSF-1 gene (on 1p13). The majority of cells in the tumor mass are non-neoplastic inflammatory cells that do not express CSF-1 but are attracted to the tumor site because of their expression of the receptor, Colony stimulating factor 1 (CSF1R).

Both PVNS and GCT-TS are rare, with an estimated annual incidence of 1.8 cases per million and 9.2 cases per million, respectively, in the US.[2] In a review of a Scottish hospital case series, Monaghan and coworkers suggested an incidence of 0.2 cases of GCT-TS per 10,000 in the EU.[3] Similarly, Ushijima et al.[4] described an incidence of 0.25 cases per 10,000 in Kyushu, Japan, while a paired study suggested a PVNS incidence of 0.06 per 10,000.[5] Patients are commonly diagnosed in their 20s to 50s, and the disease affects men and women equally.[2,6]

PVNS and GCT-TS are challenging diseases to manage. The current standard of care is surgical resection of the tumor as completely as possible in order to: (1) reduce pain, stiffness, and joint destruction caused by the disease process; (2) improve function; and (3) minimize the risk of recurrence. Patient outcome following surgery depends on

multiple factors, including the location and extent of disease, thorough diagnostic evaluation, and the technical skill of the surgeon. The overall recurrence rate for patients with focal localized disease is low, ranging from 0% to 6%; however, in patients with diffuse forms of the disease, recurrence is considerably more common, estimated to be in the range of 40%. Diffuse disease carries a significant risk of multiple recurrence, and affected patients often have more extensive involvement and a poorer likelihood of success with surgery. Surgical resection may involve removal of major tendons, neurovascular structures, or limbs, leading to significant postsurgical morbidity.

Currently, there are no systemic agents approved for the treatment of PVNS or GCT-TS. Products that are being evaluated in PVNS and GCT-TS include: imatinib (Gleevec) [7,8] a multi-kinase inhibitor that targets Bcr-Abl tyrosine kinase yet also shows activity against CSF1R; nilotinib (Tasigna), a second-generation drug based on imatinib [9], a macrophage colony stimulating factor antibody; and a humanized monoclonal antibody that targets CSF1R.[10]

### 1.1.2. Pexidartinib (PLX3397)

Pexidartinib is a novel orally active small-molecule tyrosine kinase inhibitor that targets CSF1R, Kit (the receptor for stem cell factor), and oncogenic fms-like tyrosine kinase 3 (Flt3), the receptor for Flt3 ligand, but remains highly selective versus other kinases. It is hypothesized that since PVNS and GCT-TS tumors cause pathology by secreting high levels of CSF-1, pexidartinib should oppose disease progression by directly targeting the CSF1R that drives the target cells. Inhibition of this pathogenetic pathway should block both the neoplastic cells that express CSF-1, which are often in the minority, and the non-neoplastic inflammatory cells that comprise most of the tumor mass and do not express CSF-1 but are attracted to the tumor because of their expression of CSF1R.

## 1.2. Nonclinical Studies

When screened in vitro against a broad panel of 230 kinases, pexidartinib shows potent and selective inhibition against its intended targets: CSF1R, Kit, and activated Flt3. Pexidartinib also blocks osteoclast differentiation and cell growth of CSF-1-dependent cell lines. Although nonclinical animal models of PVNS are not available, pexidartinib has shown the ability to block CSF1R activity in a variety of in vivo models. pexidartinib shows dose-dependent inhibition of splenomegaly in an engineered CSF1R-dependent mouse model. In the collagen-induced arthritis model, pexidartinib shows substantial efficacy by blocking the activity of macrophages and osteoclasts that infiltrate the diseased joints, reduces synovial inflammation and cartilage destruction, and reduces clinical scores for joint and digit swelling and redness even with treatment of advanced disease.

Additional detailed information regarding the nonclinical pharmacology and toxicology of pexidartinib can be found in the IB.[11]

## 1.3. Clinical Experience

Pexidartinib has been evaluated in multiple clinical studies, three have either been completed or have a report in progress: Study PLX108-03, in patients with relapsed or

refractory Hodgkin's lymphoma; Study PLX108-04, in recurrent glioblastoma multiforme; and Study PLX108-06, in subjects advanced metastatic prostate cancer. In addition, single-dose studies PLX108-11 and PLX3397-A-U114 were completed in healthy subjects. Seven ongoing studies are evaluating pexidartinib in subjects with advanced incurable solid tumors. These trials focus on PVNS (PLX108-01) [12] and PLX108-10), relapsed or refractory acute myeloid leukemia (AML) (PLX108-05), combination therapy in advanced incurable solid tumors (PLX108-07, with paclitaxel; PLX108-14, with pembrolizumab), in newly diagnosed glioblastoma multiforme (GBM) (PLX108-08, with temozolomide and radiation), and in BRAF-mutated metastatic melanoma (PLX108-09, with vemurafenib). All of these studies are open-label and uncontrolled.[11]

See IB dated 07Dec2015 for total number of subjects exposed and the clinical experiences with pexidartinib.[11] As of 31-July-2015, 485 subjects have been exposed to pexidartinib. Cumulative safety data show the most commonly reported treatment-emergent adverse events (TEAEs) (> 10%) treatment-related TEAEs have included fatigue, nausea, decreased appetite, hair color changes, diarrhea, AST increased, vomiting, anemia, dysgeusia, ALT increased, and rash. Among common treatment-related TEAEs, fatigue, increased AST and ALT, anemia, and rash occurred at Grade 3 or higher severity and at a frequency greater than 1%.[11]

Serious adverse events (SAEs) that were assessed as subjects who experienced SAEs as judged by the study Investigator as possibly or probably related to study drug have been reported across all studies. Treatment-related SAEs reported more than once include neutropenia (including febrile neutropenia), increased ALT, increased AST, pneumonia, thrombocytopenia, dehydration, pyrexia, anemia, hyponatremia, increased INR, decreased neutrophil count, rash, and maculo-papular rash.

A total of 21 deaths (excluding those attributed solely to disease progression) were recorded by 31 July 2015, which include deaths occurring after study drug discontinuation in the follow-up period for assessment of overall survival. The majority of deaths attributed to an AE were considered unrelated to study treatment and some were likely related to a complication of their underlying malignancy. Death was attributed to pexidartinib treatment by Investigators in 2 patients: Patient PLX001-06-609 with widely metastatic Erdheim-Chester disease (polyostotic sclerosing histiocytosis) died from a cerebrovascular accident (CVA) 504 days after initiating treatment with pexidartinib at 1000 mg/day (PLX108-01). The relationship of the CVA to pexidartinib was considered by the Sponsor's Medical Monitor as being unlikely due to lack of pharmacologic plausibility (i.e., nonclinical data do not suggest any mechanism for thromboembolic events); lack of similar events in the current safety database; and the presence of potential underlying predisposing clinical conditions, such as numerous old central nervous system infarcts on imaging of the brain, and bilateral internal carotid and middle cerebral artery abnormalities of the neck on computerized tomography with contrast. Patient PLX005-07-009 with AML died from cytokine release syndrome, which was reported as a Serious Adverse Reaction (SAR), 31 days after initiating treatment with pexidartinib at 3000 mg/day (PLX108-05). The fatal SAE of cytokine release syndrome was considered to be partly due to differentiation syndrome, a syndrome that can occur in patients manifesting a positive response to anti-leukemic therapy. Because this event is considered to occur

only in AML patients responding to treatment, no additional safety assessments were recommended.

No safety signals in vital signs, physical examinations, or electrocardiograms (ECGs) (including reports of potentially clinically significant QT prolongation) have been identified. At pexidartinib doses of ≥ 600 mg/d, transient increases in AST and/or ALT have been observed across all clinical studies. In uncontrolled clinical studies of single agent pexidartinib and in combination with other anti-cancer agents, bone marrow suppression with leukopenia (neutropenia and/or lymphopenia), anemia and thrombocytopenia, either alone or with pancytopenia, has been observed. In addition, elevations of liver transaminases and bilirubin have also been observed in studies with pexidartinib.

The current version of the IB is dated 26Oct2016.

### 1.3.1. Subjects with PVNS/GCT-TS Treated in Study PLX108-01

Study PLX108-01, an ongoing open-label uncontrolled dose-escalation study in subjects with advanced incurable solid tumors, has provided preliminary data for clinical improvement with pexidartinib in a cohort of PVNS/GCT-TS subjects treated in that study's extension phase. To be eligible for the PVNS/GCT-TS cohort, subjects were required to have a histologically confirmed diagnosis of inoperable progressive or relapsing PVNS/GCT-TS or have a potentially resectable tumor requiring mutilating surgery, and demonstrated progressive disease within the previous 12 months. Subjects were given pexidartinib at the recommended Phase 2 dose of 1000 mg/d administered as a split dose (600 mg in the morning, 400 mg in the evening), and they were to continue treatment until tumor progression or unacceptable toxicity. Enrollment is ongoing.

MRI was performed every two cycles (8 weeks); evaluable scans were assessed by a central musculoskeletal radiologist blinded to chronology using a novel Tumor Volume Score (TVS) developed specifically for PVNS/GCT-TS. This method was developed for PVNS/GCT-TS and used an extension of the 4-point synovitis scale of the well-established and widely used Outcome Measures in Rheumatology Clinical Trials Rheumatoid Arthritis MRI Score (RAMRIS) erosion scale, originally developed for assessing rheumatoid arthritis of the hands and wrists[13], and the Whole Organ MRI Score (WORMS)[14] originally developed for assessing osteoarthritis. The percent change in the TVS is calculated for each post-baseline MRI scan. Responder criteria were defined as follows:

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| Complete Response (CR): | Lesion completely gone by the end of the study. |
| Partial Response (PR): | ≥ 50% decrease in volume score relative to baseline. |
| Progressive Disease (PD): | ≥ 30% increase in volume relative to the lowest score during the study whether at baseline or some other visit. |
| Stable Disease (SD): | Does not meet any of the previous criteria based on score during the study. |

Subject Characteristics and Tumor Responses

Twenty-three subjects in this cohort received at least one dose of study treatment. Median duration of treatment was 244 days, and the mean duration of treatment was 254 days (range, 15 to 585 days). Among those who withdrew from the study, reasons for discontinuation were subject decision (three subjects), adverse event (two subjects; pain in the non-PVNS extremity and fatigue, respectively), noncompliance (one subject), and disease progression (one subject). A slight majority was female and most was white. The knee was the most common site of involvement. Prior to study enrollment, 18 of the subjects had undergone surgery and four had been treated with imatinib or nilotinib.

As of 30-Jun-2014, an interim analysis data cutoff date, 14 of 23 subjects had a baseline and at least one post-baseline MRI that was radiologically evaluable and assessed by central readers using a TVS method (Plexxikon; data on file). The radiologically non-evaluable subjects consisted of three subjects with no post-baseline MRI, four subjects with metallic artifact, and one subject each with unevaluable tumor or lymph node CT only (metastatic disease).

Most of the evaluable subjects had a rapid decline in TVS that was maintained over time. Eleven (79%) achieved a partial response, and three (21%) experienced stable disease as a best response by TVS criteria. None had a complete response or progressive disease. Mean tumor size reduction was 61%. While metastatic PVNS/GCT-TS are quite uncommon, one subject with metastatic disease was enrolled in the study but was not evaluable by TVS. This subject had stable disease for 8 months before progressing at a metastatic focus. From this dataset, this subject is the only one who progressed while on therapy.

All 23 subjects experienced at least one adverse event (AE) considered by the Investigator to be possibly or probably related to pexidartinib. The most frequently reported treatment-related AEs were hair color changes, fatigue, nausea, decreased appetite, diarrhoea, vomiting, anaemia, rash, periorbital edema, and dysgeusia.[11]

Treatment-related AEs of Grade ≥ 3 severity was reported in eight subjects: anemia (one subject), neutropenia (one subject), hyponatremia (two subjects), elevated ALT and AST (two subject), fatigue (one subject) and diarrhea (one subject). Two subjects experienced three AEs that led to hospitalization: one subject had Grade 3 cholecystitis and Grade 4 hyponatremia, and the other had Grade 3 acute renal failure. In the subject with cholecystitis and hyponatremia, the cholecystitis was judged as unrelated to treatment while the hyponatremia was judged to be treatment related. The events were treated and resolved. This subject left the study because of noncompliance. In the subject who experienced acute renal failure, the event occurred in the context of an untreated urinary tract infection and dehydration; it was treated, resolved, and judged as unrelated to the study treatment. The subject resumed study treatment without incident. No subjects in this cohort died during the study.

Approximately half of the subjects experienced frequent transient increases in AST and/or ALT. Most of these elevations were of Grade 1 severity, remained stable or returned to normal with continued dosing, and were not considered to be AEs. Three subjects had Grade 3 ALT and/or AST elevations that resolved to Grade 1 or less after

drug holidays; in two of these three subjects, dosing was resumed. One subject had a Grade 2 AST elevation (with a Grade 1 ALT elevation) that resolved to Grade 1 or less with continued dosing. In all cases, total bilirubin was normal.

Further details on the clinical experience with pexidartinib can be found in the IB.[11]

## 1.4. Study Rationale

This study will be conducted in two parts. Part 1 will be a double-blind randomized placebo-controlled Phase 3 trial in subjects with symptomatic PVNS or GCT-TS for whom surgical resection would be associated with potentially worsening functional limitation or severe morbidity (locally advanced disease). Eligible candidates will be randomized in a 1:1 ratio to receive either pexidartinib or placebo twice daily for 24 weeks. The double-blind and randomized design will allow adequate comparison of pexidartinib with a control group. Placebo was selected as the control group because there is no existing non-surgical treatment that is accepted as standard of care for PVNS/GCT-TS. Surgical treatment cannot be used as a control treatment because the patient population includes those for whom surgery is associated with potentially worsening function limitation or severe morbidity. Both the placebo and pexidartinib treatment groups will receive the usual supportive standard of care, eg, analgesic medications.

Subjects will be started with 1000 mg/d pexidartinib or matching placebo, ie five capsules, in Part 1. It will be split into a morning dose of two capsules (400 mg pexidartinib or matching placebo) and an evening dose of three capsules (600 mg pexidartinib or matching placebo) and will be given in the fasting state (no food for 1 hour before and 2 hours after dosing, with a low-fat snack if needed). Beginning on P1-C1D15, the maximum daily dose will be reduced to four capsules (800 mg pexidartinib or matching placebo) if it has not already been reduced to that amount or less. When subjects begin Part 2, they will continue taking the same number of capsules but of open-label pexidartinib, also split into a morning and an evening dose. Selection of the pexidartinib starting dose of 1000 mg/d and the split-dose administration schedule is based on data from subjects with solid tumors, including the small cohort of subjects with PVNS who received pexidartinib in Study PLX108-01, a Phase 1 trial. In the dose-escalation portion of that trial, two subjects receiving 1200 mg/d, administered as a split dose, experienced dose-limiting toxicities: anemia, neutropenia, and syncope in one subject and elevated AST in the other. For this reason, 1000 mg/d given as a split dose was selected as the maximum tolerated dose and the recommended Phase 2 dose.

Data from the PVNS cohort in Study PLX108-01, a Phase 1 trial, suggest that some subjects may require dose modification. While dose levels at and above 600 mg/d have similar safety profiles, subjects who had difficulty tolerating 1000 mg/d as a split dose were able to tolerate 600 or 800 mg/d. Since approximately half of the PVNS subjects in Study PLX108-01 required a dose reduction to at least 800 mg/d within the first 2 cycles (Plexxikon, data on file), in this study subjects will be required to reduce their dose, from 1000 mg/d or matching placebo to a maintenance dose of 800 mg/d of pexidartinib or matching placebo, beginning on P1-C1D15. A dose reduction algorithm will allow subjects to further reduce the dose of pexidartinib or matching placebo in increments of

one capsule, as needed (Section 5.3). Those unable to tolerate pexidartinib 400 mg/d or matching placebo will be discontinued.

The subjects to be studied in this trial are those with symptomatic nonmetastatic PVNS or GCT-TS in whom surgical resection is associated with potentially worsening functional limitation or severe morbidity. The use of pexidartinib, a selective kinase inhibitor that targets CSF1R (the receptor for colony stimulating factor 1, which is overexpressed in PVNS/GCT-TS)[15], offers a promising new therapeutic option for patients with this diagnosis who would not be adequately treated with surgery, the existing standard of care.

The 24-week duration of treatment was selected on the basis of the preliminary data from Study PLX108-01. Almost all of the decreases in TVS have been observed before the end of C6, ie, before the end of 24 weeks of pexidartinib treatment. Accordingly, the duration of Part 1 is ethically limited to 24 weeks to keep the placebo-controlled portion as short as possible and enable the placebo-treated subjects to receive pexidartinib as soon as possible in Part 2; up to that point in the study, the subjects in the placebo arm will be receiving background standard of care.

### 1.4.1. Study Purpose

The purpose of this study is to evaluate the efficacy and long-term safety, pharmacokinetics, and pharmacodynamics of pexidartinib treatment in subjects with symptomatic PVNS/GCT-TS. The primary efficacy endpoint is the proportion of subjects who achieve a complete or partial response at the Week 25 visit based on centrally read MRI scans and Response Evaluation Criteria in Solid Tumors, v. 1.1 (RECIST 1.1).[16]

## 1.5. Risks and Benefits for Study Subjects

In the Good Laboratory Practice repeat-dose toxicology studies consisting of up to 13 weeks of pexidartinib dosing, test article-related adverse effects were noted in testes (testicular spermatogonia reduction), ovaries (ovarian follicular degeneration), bone and bone marrow, hematology and lymphoid changes; these changes are consistent with the pharmacological mechanism of action of pexidartinib. All test article-related findings were partially or fully reversible.[11] Potential dose-related changes in bone marrow function can be monitored by peripheral cell count and differential counts. Because of the effects on reproductive organs, subjects will be monitored for changes in luteinizing hormone (LH), follicle-stimulating hormone (FSH), and other sex-specific hormone levels.

Effects on embryofetal development have been observed in both rat and rabbit toxicology studies up to 13 weeks. Dose level of 10 mg/kg/day was considered to be the NOAEL for embryofetal development when pexidartinib was administered orally by gavage to pregnant Sprague-Dawley rats. Dose of 20 mg/kg/day was considered to be the NOAEL for both reproduction in dams and embryo/fetal development. It was judged that pexidartinib was teratogenic in rabbits in the present study. Subjects in the study will be required to use adequate birth control during the study and for 90 days after the last dose of study treatment administered during study participation.

Findings in the nonclinical canine safety pharmacology study suggest that pexidartinib may have a negative inotropic effect. Subjects will be monitored for changes in ejection fraction with cardiac echocardiograms.

In clinical evaluation to date, the most common TEAEs of all grades have been fatigue, decreased appetite, nausea, vomiting, anemia, hair color depigmentation, and diarrhea. In a proportion of all subjects treated with pexidartinib, liver transaminases increased to approximately 1.5 × upper limit of normal (ULN) during the first cycle, followed by partial resolution during subsequent dosing. In some instances, the increase in liver enzymes may require dose hold or modification. Dosing modification guidance is included within the protocol for AE monitoring (Section 5.3). Liver function (clinical chemistry), renal function (clinical chemistry), and heart electrophysiology (QTc evaluation) will be monitored during this study.

Based on TEAE reports of increased INR in subjects on warfarin who receive pexidartinib, subjects receiving warfarin should be carefully monitored when starting pexidartinib, and warfarin doses should be adjusted if an increase in INR is noted.

More detailed and updated information regarding clinical safety data can be found in the IB.[11]

PVNS and GCT-TS are progressive diseases with no ideal or standardized treatments. No systemic treatments and no treatments specifically directed to the recently identified pathogenetic pathways have been approved for these diseases. Although the standard of care is surgery, guidelines and evidence-based data for the timing and extent of surgical intervention are lacking.[17] Surgical outcomes, even when curative, may result in marked patient morbidity as reflected in post-operative pain, limitation in function, and cosmetic disfigurement.[18] In extreme or recurrent cases, the tumor may be aggressive and require limb amputation.[19] The use of pexidartinib, a selective kinase inhibitor that targets CSF1R (which is overexpressed in PVNS and GCT-TS)[15], offers a promising new therapeutic option for patients with PVNS or GCT-TS.

In summary, given the acceptable safety profile of the pexidartinib at the selected dose and the promising Phase 1 data in subjects with PVNS/GCT-TS, the potential for a positive benefit/risk profile is assumed for the Phase 3 study.

## 1.6. Updated Risk Information and Change in Study Conduct

During the conduct of this study, updated safety information became available including two SAEs in this study consistent with cholestatic liver dysfunction. There were an estimated 80 subjects who had been exposed to pexidartinib at the time of this finding. The initial case, a 75 year old woman with few risk factors, experienced hyperbilirubinemia for 2.5 months (ongoing), requiring study treatment discontinuation, hospitalization and two liver dialysis procedures. A liver biopsy showed cholestasis and ductopenia. The second case, a 52 year old male with few risk factors, had grade 4 liver enzyme increase concurrent with hyperbilirubinemia, which resolved on study treatment discontinuation without further measures. Both cases were not re-challenged with the study treatment.

Five cases of this pattern of liver dysfunction have been observed in other pexidartinib trials, both in monotherapy and combination therapy. In total there are now 7 cholestatic/mixed type of liver dysfunction cases reported among approximately 550 subjects. In addition to the above ENLIVEN study cases, prolonged hyperbilirubinemia (> 8 months, ongoing) occurred in one case and two other cases took 2-3 months to resolve. All cases occurred between 14 and 57 days of the start of pexidartinib treatment, suggesting a higher risk within the first 8 weeks of treatment. Three of the 7 cases had liver biopsy showing cholestasis and ductopenia. More detailed and updated information regarding clinical safety data can be found in the IB.[11]

In response to the emergence of the two cases of potential cholestatic liver injury, the study Data Monitoring Committee (DMC) was requested to review the unblinded safety data related to these cases, other safety data from this study, and safety data for similar cases in other studies. The DMC recommended safety measures that changed the conduct of this study to enhance the protection of subjects. The following measures were implemented effective on 30 Sep 2016:

1. Enrollment was stopped. No new subjects may start study treatment. Subjects in screening and randomized subjects who have not started treatment must be discontinued.
2. Subjects on placebo in Part 1 are no longer allowed to enter Part 2 to receive open-label pexidartinib. After completion of the end of Part 1 assessments (Part 1 Completion visit/Early Termination visit), subjects who wish to continue onto the open label part of this study (Part 2) will be unblinded and those on placebo will be discontinued; subjects on pexidartinib in Part 1 may continue into Part 2 to continue to receive pexidartinib.
3. Investigators and subjects must be informed of the new safety information and decide whether to continue in the study. If, after consultation with the subject, it is deemed to be in their best interest to continue treatment, the subject must be re-consented.
4. The frequency of liver function testing is increased, and gamma-glutamyl transpeptidase (GGT) is added to the laboratory panel.

Updated hepatic safety risk information as of December 2017; please consult the IB for more information. Hepatotoxicity is an important adverse drug reaction. Elevations of liver transaminases and bilirubin have been observed in studies with pexidartinib, together with cases of drug-induced cholestasis. Cases of cholestasis have been observed in the first 8 weeks and have generally resolved with treatment discontinuation; however, some cases have been severe, with a protracted course requiring liver dialysis and, in 1 case, transplantation. Hepatotoxicity may be fatal. One fatal case with ongoing cholestatic liver injury at the time of death has been reported. Monitor patients closely as defined in the protocol. Protocol-defined dose reductions and discontinuations of pexidartinib, increased frequency of laboratory monitoring, and reporting of findings should be followed. In addition, rechallenge with pexidartinib should not be attempted without prior discussion with the Sponsor's Medical Monitor.

# 2. STUDY OBJECTIVES AND HYPOTHESIS

## 2.1. Study Objectives

The primary objective of this study is to compare the response rate of pexidartinib with that of placebo per RECIST 1.1 at Week 25 in subjects with symptomatic, locally advanced PVNS or GCT-TS.

The secondary efficacy objectives are to evaluate: (i) Patient-reported Outcomes (PROs), including the Brief Pain Inventory (BPI) Worst Pain Numeric Rating Scale (NRS) item, Patient-reported Outcomes Measurement Information System (PROMIS) Physical Function Scale, and Worst Stiffness NRS item, at Week 25; (ii) response based on TVS at Week 25; (iii) range of motion at Week 25; and (iv) duration of response.

Other objectives are to evaluate (i) other measures of efficacy, (ii) long-term safety, (iii) pharmacokinetics (PK), and (iv) pharmacodynamics (PDy) of pexidartinib in treated subjects.

## 2.2. Study Endpoints

### 2.2.1. Primary Efficacy Endpoint

The primary efficacy endpoint is the proportion of subjects who achieve a complete or partial response at the Week 25 visit based on centrally read MRI scans and RECIST 1.1.

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

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

No confirmation (ie, CR or PR at the subsequent MRI assessment) will be required for a CR or PR per RECIST 1.1 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 time point is based on the combination of responses for target lesions, and the presence or absence of one or more new lesions. For the purpose of this protocol and in alignment with RECIST 1.1, determination of the tumor response status for each subject in Part 1 with respect to the primary efficacy endpoint is shown in Table 2.1.

To be considered a response, a tumor must meet the criteria for response and must have documented non-progression at Week 25. A tumor that achieves PR at Week 13 followed by neither sufficient shrinkage to qualify for CR nor sufficient increase to qualify for PD (ie, non-CR/non-PD/non-NE) at Week 25 will be considered a responder for the primary efficacy endpoint.

**Table 2.1: Definitions of Response for the Primary Efficacy Endpoint**

| Time Point Response at Week 13 (P1-C4D1 visit) | Time Point Response at Week 25 (Part 1 Completion visit) | 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, or NE | NE | Non-response (NE) |
| PD | Any | Non-response (PD) |
| NE | CR or PR | Response (CR or PR) |
| NE | SD or PD | Non-response (SD or PD) |

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.

For the entire study, centralized review of the scans will be performed by readers blinded to treatment assignment and other clinical study data. Scans will be obtained according to the MRI Imaging Charter. The imaging charter for this study describes the image acquisition standards and methodology to be used as well as the standards for image interpretation.

RECIST 1.1 has been used as a primary outcome measure in Phase 3 trials of several targeted therapies for the treatment of solid tumours (eg, crizotinib for advanced non-small cell lung cancer, dabrafenib for BRAF V600 mutation-positive unresectable or metastatic melanoma) and is supported by feedback from regulatory agencies for this study. Eisenhauer et al, who proposed the revised RECIST guideline (version 1.1), noted the importance of future work in moving from anatomic unidirectional assessment of tumour burden to either volumetric anatomical assessment or functional assessment with positron emission tomography scan or MRI.[16] However, they concluded that use of promising newer approaches in these areas would require appropriate clinical validation studies.

### 2.2.2. Secondary Efficacy Endpoints

The following evaluations comprise the secondary efficacy endpoints:

1. Mean change from baseline in range of motion of the affected joint, relative to a reference standard for the same joint, at the Week 25 visit
2. Proportion of responders based on centrally evaluated MRI scans and TVS at the Week 25 visit
3. Mean change from baseline score in the PROMIS Physical Function Scale at the Week 25 visit
4. Mean change from baseline score in the Worst Stiffness NRS item at the Week 25 visit
5. Proportion of responders based on the BPI Worst Pain NRS item and analgesic use by BPI-30 definition (as defined in Section 7.6.2)
6. Duration of response (CR or PR) based on MRI and RECIST 1.1
7. Duration of response (CR or PR) based on MRI and TVS

The PRO instruments to be used as secondary outcome measures were selected on the basis of a process that involved:

1. A targeted literature review
2. Discussions with four clinical experts with extensive experience managing PVNS/GCT-TS
3. A qualitative study carried out by the Sponsor to identify the key relevant concepts and confirm consistency with the literature
4. Evaluation of a number of symptom instruments that were considered of potential relevance and could be adapted for use in assessing symptoms in PVNS/GCT-TS

Reviews of the literature, input from clinical experts, and subject cognitive debriefing supported the content and relevance of the BPI Worst Pain NRS Item. Subjects in the qualitative study often reported pain as a common and dominant symptom that varied on a daily basis. For the BPI Worst Pain NRS item, subjects are asked to recall their worst pain at the site of their tumor in the past 24 hours. The brief recall period of 24 hours could provide information based on daily assessment, and the instrument is applicable to any tumor location. Assessments could be combined and summarized over a time period longer than 24 hours to yield more accurate estimates of subjects' experiences of pain for weekly periods.

Selection of stiffness and physical functioning as secondary endpoints was also based on a review of the literature, discussions with four clinical experts, and input from subjects with PVNS or GCT-TS. Stiffness was mentioned by 16 of the 22 participants (73%), including those with upper- and lower-extremity tumors, and specific impacts on functioning were mentioned by all participants either in the context of associations with specific symptoms or as a result of limitations to range of motion due to the tumors (Plexxikon, data on file).

Specifically, the PROMIS Physical Functioning items and a Worst Stiffness NRS item were selected on the basis of (i) specific recommendations from the clinical experts and (ii) the alignment of the concepts measured by these instruments with the symptom experiences reported by subjects with PVNS/ GCT-TS in the qualitative study.

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

Stiffness will be evaluated using a Worst Stiffness NRS item. Similar to the BPI Worst Pain item, the Worst Stiffness NRS item uses a 24-hour recall period. Subjects are asked to recall their worst stiffness at the site of their tumor in the past 24 hours. Like the BPI Worst Pain item, assessments can also be combined and summarized over a longer time period to yield more accurate estimates of subjects' experiences of stiffness for weekly periods.

TVS is a semi-quantitative MRI scoring system that describes tumor mass and is an extension of the 4 point synovitis scale of the well-established and widely used multi-feature score RAMRIS, originally developed for rheumatoid arthritis[13], and WORMS, originally developed for osteoarthritis.[14] The extended scale, the TVS, will be based on 10% increments of the estimated volume of the maximally distended synovial cavity or tendon sheath involved. Thus, a tumor that is equal in volume to that of a maximally distended synovial cavity or tendon sheath will be scored 10, whereas a tumor that is 70% of that volume will be scored 7, a tumor that is twice the volume of the maximally distended synovial cavity or tendon sheath will be scored 20, and so on. A score of "0" means no evidence of tumor.

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

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

The cutoffs of 50% for PR and +30% for PD were developed in consultation with clinical experts. This magnitude of reduction was observed in a majority of evaluable subjects with PVNS from the Phase 1 study of pexidartinib (Section 1.3.1). The tumor response status on this endpoint in Part 1 is determined in a way similar to that for the primary efficacy endpoint (Table 2.1).

To minimize bias and reduce variability, all MRIs will be read centrally in a blinded manner for RECIST 1.1- and TVS-based responses according to the separate MRI Imaging Charter.

Treatment effects on physical functioning will be assessed by an objective range of motion assessment performed by a qualified independent third party such as an orthopedic surgeon or a physical therapist blinded to treatment assignment, and when possible, to investigational drug name and to study protocol. This assessment uses standard goniometers and has been standardized according to American Medical Association disability criteria.[20] Details of this analysis are described in Section 7.6.2.

### 2.2.3. Additional Endpoints

Additional endpoints to be analyzed at appropriate time points include:

- The long-term safety of pexidartinib in treated subjects, assessed from physical examination findings, vital sign data, 12-lead ECGs, echocardiograms, AEs, serum chemistry, hematology, coagulation tests, urinalysis, and hormone testing (as applicable)
- Proportion of responders on the BPI Worst Pain NRS item and analgesic use by BPI-2p definition (as defined in Section 7.6.3)
- Proportion of responders on the BPI Worst Pain NRS item and analgesic use by BPI-50 definition (as defined in Section 7.6.3)
- Proportion of responders on the Worst Stiffness NRS item
- Proportion of responders on the PROMIS Physical Function Scale
- Mean change from baseline in the BPI Worst Pain NRS item
- Patient Global Impression of Change item for tumor-related stiffness and Patient Global Rating of Concept item for ability to carry out every day physical activities
- Duration of BPI-based symptom response, analyzed for BPI-30, BPI-50 and BPI-2p
- Results of the Surgical Assessment Questionnaire in Part 1
- Response based on the change in the sum of the short-axis dimension (SSD) of the tumor on MRI
- Proportion of subjects receiving surgical resection of their tumor by 25 weeks, 49 weeks, 73 weeks, and 97 weeks of pexidartinib treatment

In addition to standard RECIST 1.1, which is based on the longest unidimensional measurement, an exploratory endpoint will be the response based on centrally read MRI and the SSD of the tumor, hereafter referred to as “modified RECIST 1.1–SSD.”

Short-axis measurements will be made perpendicular to a reproducible adjacent landmark such as the femoral bone or a tendon, where the tumor dimension appears greatest and yet confidently measurable. Measurement of this site will be repeated on the other visits. The

tumor response status on this endpoint in Part 1 will be determined in a way similar to that for the primary endpoint Table 2.1.

Amount of joint/tissue damage (eg, bone erosion, bone edema, cartilage loss) assessed on MRI based on adaptations of the RAMRIS and WORMS:

Bone erosion will be scored based on the RAMRIS-erosion scale originally developed for assessing rheumatoid arthritis of the hands and wrists.[13] 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[14] or to each articular bone in the ankle/foot or elbow. Articular bone is defined as bone within 1 cm of the articular surface.

Bone edema and cartilage loss will be scored based on WORMS in the same regions as bone erosion assessments.

- Analgesic use expressed as morphine-equivalent doses in Part 1
- EuroQol five-dimensional descriptive system (EQ-5D-5L) parameters in Part 1
- Major healthcare resource use (HCRU) and productivity in Part 1
- Duration of response based on MRI and modified RECIST 1.1-SSD
- Response based on the most disturbing symptom of pain, stiffness, or compromised ability to carry out everyday activities

The data from this study will be analyzed using a pooled population pharmacokinetic (PopPK) approach using nonlinear mixed effects modeling. PK parameters will include apparent clearance and volume of distribution along with transfer rate constants such as absorption and elimination rates. Additionally, based on post-hoc Bayesian methods, estimates of exposure such as $C_{max}$, $C_{trough}$, $C_{av}$ and $AUC_{ss}$ may also be reported.

Plasma will be analyzed for pexidartinib PDy markers and for exploratory markers of monocyte or macrophage activities, including CSF-1 and adiponectin. When available and consented, archival surgical tissue from PVNS or GCT-TS tumors will be collected for exploratory analysis related to pexidartinib and/or disease.

## 2.3. Study Hypothesis

Pexidartinib is safe and more efficacious than placebo when administered to subjects with symptomatic, locally advanced PVNS/GCT-TS.

# 3. STUDY DESIGN

## 3.1. Overall Plan

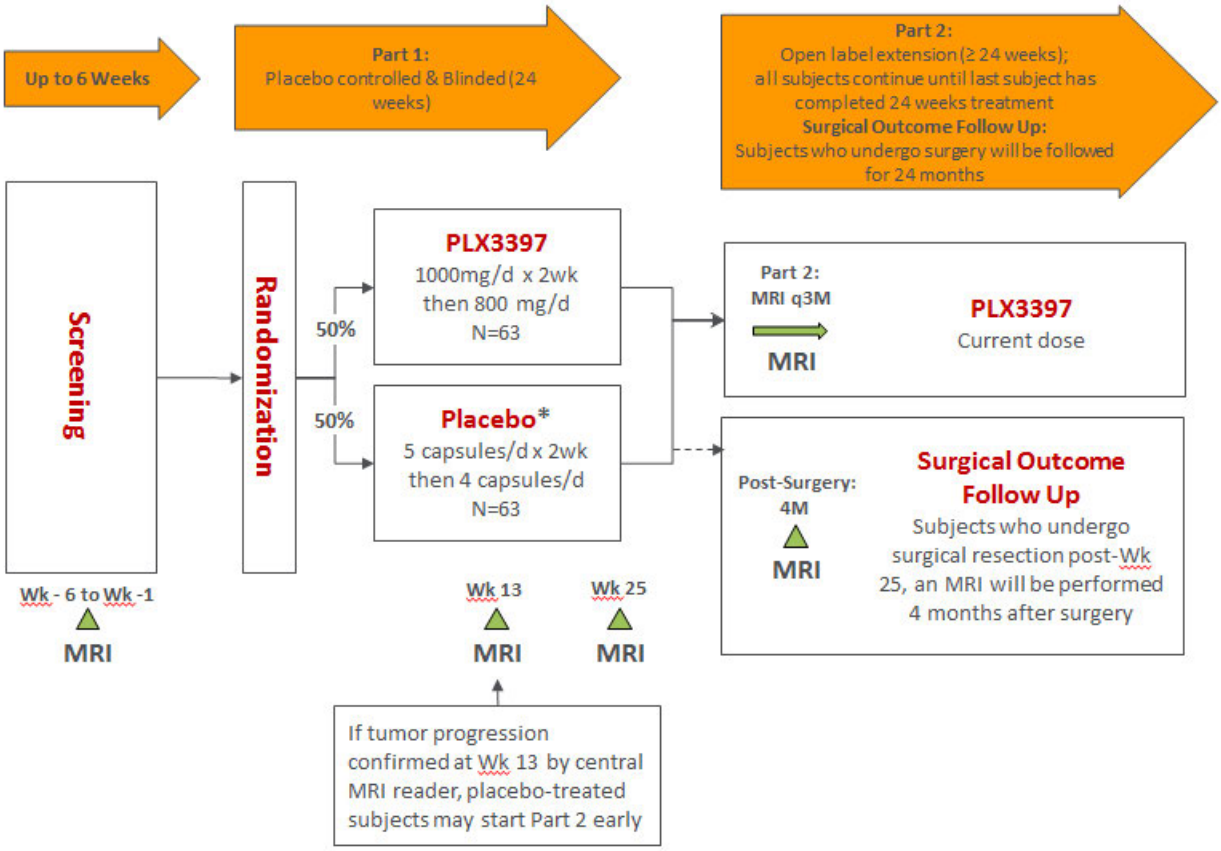
This trial is a two-part multi-center Phase 3 study in subjects with symptomatic PVNS or GCT-TS for whom surgical resection would be associated with potentially worsening functional limitation or severe morbidity (locally advanced disease). In Part 1, the double-blind phase, eligible candidates will be centrally randomized in a 1:1 ratio to receive either pexidartinib or placebo for 24 weeks. Randomization will be stratified by US versus non-US sites and by upper extremity versus lower extremity involvement.

Study treatment will be administered twice a day, every day. For the first 2 weeks in Part 1, subjects will take two capsules in the morning and three capsules in the evening, 1000 mg/d pexidartinib or matching placebo. Thereafter, dosing will be reduced to two capsules in the morning and two capsules in the evening, 800 mg/d pexidartinib or matching placebo. Subjects who had a dose reduction during the first 2 weeks will continue treatment at their reduced dose. Each treatment cycle will be 28 days in duration and subjects will be treated for up to 6 Cycles. Dose reductions, interruptions, and re-escalations after previous reductions for toxicity are permitted according to pre-specified guidelines. Those subjects who complete Part 1 (ie, complete 24 weeks of dosing and the Week 25 assessments) will be eligible to advance to Part 2, a long-term treatment phase where all subjects will take up to four capsules per day (800 mg/d) of open-label pexidartinib. Effective 30 Sep 2016, subjects on placebo are no longer allowed into Part 2 to receive open-label pexidartinib.

MRIs will be performed at Week 13 (Cycle 4, Day 1 visit of Part 1 [P1-C4D1]) and Week 25. If disease progression is indicated clinically or by local radiologic assessment according to RECIST 1.1 at or after Week 13 but before Week 25, the Investigator may request a central review for evaluation of disease progression. Any disease progression before Week 25 must be verified by a central MRI reading. If a central reading confirms RECIST 1.1-defined disease progression, treatment assignment will be unblinded, and subjects receiving placebo will be eligible for early entry into Part 2 of the study. Effective 30 Sep 2016, subjects receiving placebo will be discontinued instead of being eligible to enter Part 2. Subjects receiving pexidartinib will be discontinued from the study unless the Investigator and the Sponsor's Medical Monitor judge that the subject would potentially benefit from continued treatment with pexidartinib. For those subjects who undergo surgical resection after Week 25, an MRI will be performed 4 months after surgery.

Part 2 will continue until all subjects have either reached at least the Week 49 visit, ie, an additional 24 weeks of study treatment beyond the placebo-controlled phase, or withdrawn from the trial (Figure 3.1). As in Part 1, dose reductions, interruptions, and re-escalations after previous reductions for toxicity are permitted according to pre-specified guidelines. Subjects who complete Part 2 will be eligible to continue pexidartinib treatment for study of longer efficacy and safety follow-up assessed per the schedule in Part 2 or to enter a separate protocol to continue receiving pexidartinib.

**Figure 3.1: Study Schematic***




* Effective 30 Sep 2016, subjects on placebo are no longer allowed into Part 2 to receive open-label pexidartinib.

All MRI scans will be assessed by central readers blinded to treatment assignment and other clinical study data during both Parts 1 and 2 of the study, according to procedures outlined in a separate Imaging Independent Review Charter. The MRI report will not be provided in real-time unless requested by the Investigator. Results of the baseline MRI scan will be used to qualify a candidate. During Part 2, if indicated, Investigators should request confirmation of radiologic disease progression by central read. Otherwise, central reads of MRI scans may be performed during or after the subject has completed the study. The MRI scan for subjects who undergo surgical resection will be performed 4 months after surgery. Details of MRI requirements and data collection will be described in the MRI Procedure Manual.

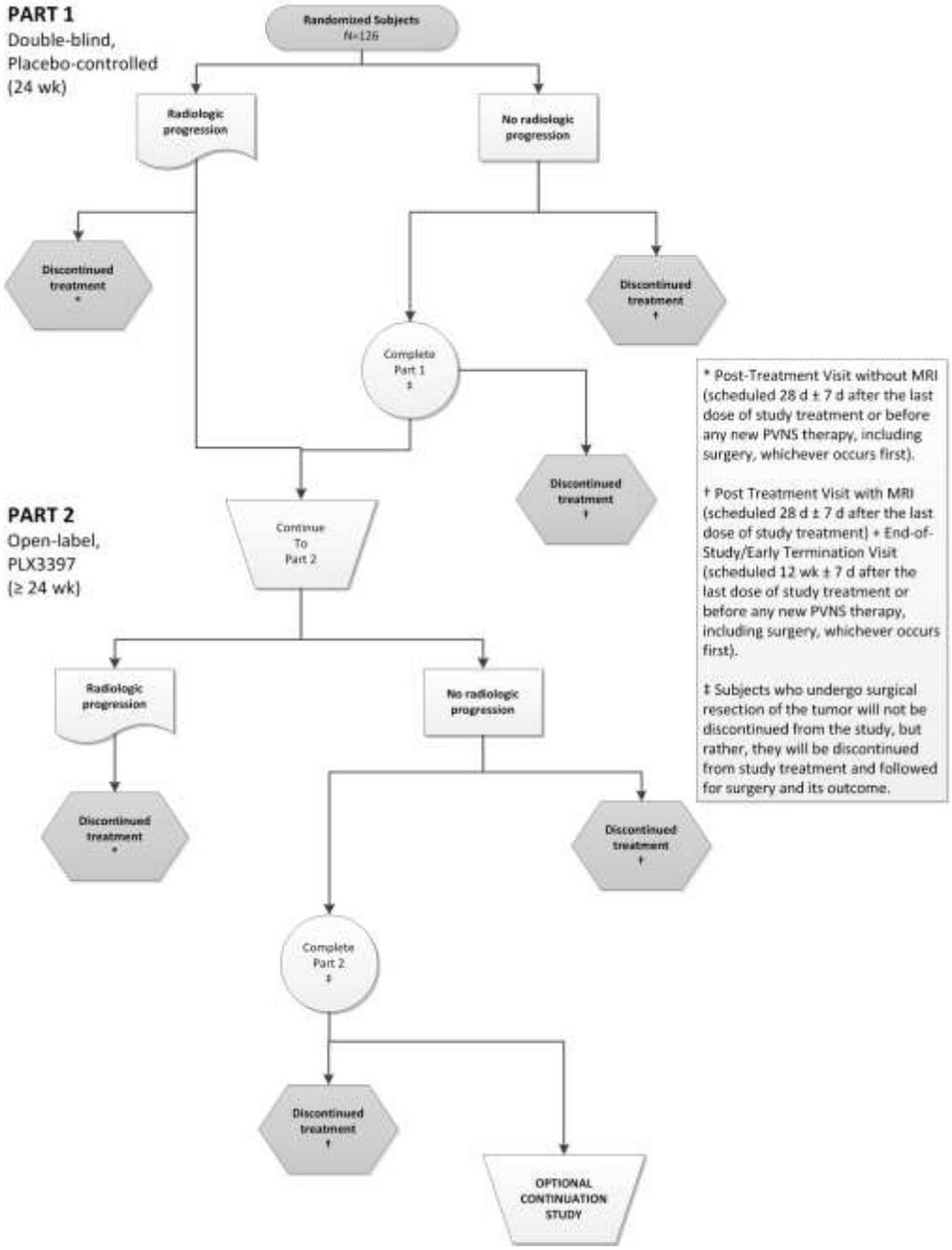
A range-of-motion assessment in the affected joint or tumor location will be performed by an independent and blinded third party assessor at specified time points. The BPI Worst Pain NRS item, physical function items from the PROMIS item bank (PROMIS Physical Function Scale), and other PRO measures will be administered according to the Study Reference Manual.

For statistical analysis of endpoints at the end of Part 1, a clinical data cut-off date will be defined for the point when all randomized subjects complete or are discontinued from Part 1 with appropriate End of Part 1 follow-up. All data up to this date will be cleaned and locked. Afterwards, unblinding of database will be performed to facilitate the data analyses, including the data from the double-blind Part 1 and available data from Part 2. Such unblinding is only intended for the sponsor and the Contract Research Organization. Subjects who entered Part 2 may continue to receive open-label pexidartinib treatment. Updated analysis of Part 2 data only, in the form of summary and descriptive statistics, will be performed at the end of the trial. Additional updates between the above-mentioned cut-off and end of the trial may also be performed.

The timing and nature of post-treatment assessments are summarized in Figure 3.2. Subjects who end their study participation with no documented disease progression will undergo: (i) the 28 Day Post-treatment Visit assessment *with* an MRI 28 ± 7 days after their last dose of study treatment; and (ii) a final MRI 12 weeks ± 7 days after their last dose of study treatment or before any new PVNS/GCT-TS therapy, including surgery, whichever occurs first (the "Part 1 End-of-Study/12 Week Post-Treatment"). Subjects who wish to continue onto the open label part of this study (Part 2) will be unblinded after completion of the end of Part 1 assessments and those on placebo will be discontinued- they will not have the 28 Day Post-treatment and End-of-Study Visit assessments. The study will end with the last subject last visit. Subjects who complete Part 2 and enter a separate protocol to continue receiving pexidartinib will not be scheduled for the Post-treatment and End-of-Study Visits. Subjects who terminate the study with documented progression will undergo a post-treatment assessment (the 28 Day "Post-treatment Visit"; see Section 15.2.17 and Section 15.3.16) *without* an MRI 28 ± 7 days after their last dose of study treatment or before any new PVNS/GCT-TS therapy, including surgery, whichever occurs first.

Subjects are allowed to undergo surgical resection of their tumor after the completion of Part 1. For subjects who undergo surgical resection within 12 weeks after their last dose of study treatment, they will not have the End-of-Study Visit assessments but will follow a separate visit schedule after the decision of surgery is made. The surgery is recommended to be performed 1-3 weeks after the last dose of study treatment. Details of the surgery and its short and long term outcome will be collected. Data collection for the surgery and its outcome may continue in a separate protocol.

**Figure 3.2: Post-treatment Assessments Vary With Reason for Study Withdrawal***




* Effective 30 Sep 2016, subjects on placebo are no longer allowed into Part 2 to receive open-label pexidartinib. Subjects who wish to continue onto the open label part of this study (Part 2) will be unblinded after completion of the end of Part 1 assessments and those on placebo will be discontinued- they will not have the 28 Day Post-treatment and End-of-Study Visit assessments.

## 3.2. Number of Subjects

Approximately 126 subjects across approximately 45 study sites in the US, Canada, EU, and Australia are planned.

## 3.3. Duration of Study

Each subject will spend approximately 3 to 6 weeks in screening. Part 1 will be 24 weeks in duration for all but those who qualify (see Section 3.1) for early entry into Part 2 because of disease progression. Effective 30 Sep 2016, subjects on placebo are no longer allowed into Part 2 to receive open-label pexidartinib. The duration of Part 2 will vary among subjects, as this portion of the trial will continue until all subjects either complete 24 weeks of open-label treatment or withdraw from the study. The study will end with the last subject last visit. Subjects who complete Part 2 without experiencing progression or intolerability, or subjects who undergo surgical resection of their tumor after study treatment will be eligible to continue for longer efficacy and safety follow-up or to enter a separate protocol to continue receiving pexidartinib or for surgical data collection.

# 4. STUDY POPULATION

## 4.1. Enrollment

All subjects must provide written informed consent. During the consent process, the person obtaining consent must inform the subject of all elements of the study. Each subject must sign and date an institutional review board (IRB)/independent ethics committee (IEC)-approved informed consent form before undergoing any study procedure (including screening procedures unless the screening procedure as outlined in the Study Reference Manual is considered standard of care and was performed within 42 days of the P1-C1D1 visit). Participation in the study begins with signing and dating the informed consent form. A subject will be considered enrolled in the study when he or she has met all of the inclusion and exclusion criteria, been deemed eligible for study participation, and been randomized.

### 4.1.1. Inclusion Criteria

Each subject must meet all of the following criteria to qualify for enrollment:

1. Age ≥ 18 years.
2. A diagnosis of PVNS or GCT-TS (i) that has been histologically confirmed either by a pathologist at the treating institution or a central pathologist, and (ii) where surgical resection would be associated with potentially worsening functional limitation or severe morbidity (locally advanced disease), with morbidity determined consensually by qualified personnel (eg, two surgeons or a multi-disciplinary tumor board).
3. Measurable disease as defined by RECIST 1.1 (except that a minimal size of 2 cm is required), assessed from MRI scans by a central radiologist.
4. Symptomatic disease because of active PVNS or GCT-TS, defined as one or more of the following:
    a. a worst pain of at least 4 at any time during the week preceding the Screening Visit (based on scale of 0 to 10, with 10 representing “pain as bad as you can imagine”).
    b. a worst stiffness of at least 4 at any time during the week preceding the Screening Visit (based on a scale of 0 to 10, with 10 representing “stiffness as bad as you can imagine”).
5. Stable prescription of analgesic regimen during the 2 weeks prior to randomization.
6. During the 2 weeks prior to randomization, at least 4 of 7 consecutive days of BPI Worst Pain NRS items and Worst Stiffness NRS items completed correctly.
7. Women of childbearing potential must have a negative serum pregnancy test within the 14-day period prior to randomization. (Where demanded by local regulations, this test may be required within 72 hours of randomization.)

8. Males and females of childbearing potential are permitted in the study so long as they consent to avoid getting their partner pregnant or becoming pregnant, respectively, by using a highly effective contraception method, as described below, throughout the study and for up to 90 days after completion. Highly effective methods of contraception include: intra-uterine device (nonhormonal or hormonal), bilateral tubal occlusion, vasectomy, sexual abstinence, or barrier methods (e.g., condom, diaphragm) used in combination with hormonal methods associated with inhibition of ovulation. Women of non-childbearing potential may be included if they are either surgically sterile or have been postmenopausal for ≥ 1 year. Women who have documentation of at least 12 months of spontaneous amenorrhea and have an FSH level > 40 mIU/mL will be considered postmenopausal.
9. Adequate hematologic, hepatic, and renal function, defined by:
   - Absolute neutrophil count $\geq 1.5 \times 10^9$/L
   - Hemoglobin > 10 g/dL
   - Platelet count $\geq 100 \times 10^9$/L
   - AST/ALT ≤ 1.5 × ULN
   - Total bilirubin ≤ 1.5 × ULN
   - Serum creatinine ≤ 1.5 × ULN
10. Willingness and ability to complete the BPI Worst Pain NRS item, Worst Stiffness NRS item, PROMIS Physical Function Scale, and other self-assessment instruments throughout the study.
11. Willingness and ability to use an electronic diary.
12. Willingness and ability to provide written informed consent prior to any study-related procedures and to comply with all study requirements.

#### 4.1.2. Exclusion Criteria

Candidates with any of the following conditions or activities are ineligible for study enrollment:

1. Investigational drug use within 28 days of randomization.
2. Previous use of pexidartinib or any biologic treatment targeting CSF-1 or the CSF1R; previous use of oral tyrosine kinase inhibitors, eg, imatinib or nilotinib, are allowed.
3. Active cancer (either concurrent or within the last year of starting study treatment) that requires therapy (eg, surgical, chemotherapy, or radiation therapy), with the exception of adequately treated basal or squamous cell carcinoma of the skin, melanoma in-situ, carcinoma in-situ of the cervix or breast, or prostate carcinoma with a prostate-specific antigen value <0.2 ng/mL.
4. Known metastatic PVNS/GCT-TS.

5. Active or chronic infection with hepatitis C virus or hepatitis B virus or known active or chronic infection with human immunodeficiency virus.
6. Known active tuberculosis.
7. Significant concomitant arthropathy in the affected joint, serious illness, uncontrolled infection, or a medical or psychiatric history that, in the Investigator's opinion, would likely interfere with the person's study participation or the interpretation of his or her results.
8. Women who are breastfeeding.
9. A screening Fridericia corrected QT interval (QTcF) ≥ 450 ms (men) or ≥ 470 ms (women).
10. MRI contraindications.
11. History of hypersensitivity to any excipients in the investigational product.
12. Inability to swallow capsules.

## 4.2. Removal of Subject From Therapy

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

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

Subjects can only be considered for surgical resection after the completion of Part 1.

If a subject undergoes surgical resection of the tumor after Part 1, the study treatment is recommended to be discontinued 1-3 weeks before the surgery. The subject will be followed for surgery and its outcome and not considered as discontinued from the study. Data collection for the surgery and its outcome may continue in a separate protocol. If a subject undergoes surgical resection prior to completion of Part 1, the information about surgery and its outcome will still be collected.

### 4.2.1. Reasons for Withdrawal/Early Discontinuation

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

- AE
- Disease progression
- Subject request
- Investigator decision
- Protocol violation
- Subject noncompliance
- Pregnancy
- Study termination by the Sponsor or IRB/IEC

During Part 2, if a subject experiences radiologic progression documented by central read, the subject may either be withdrawn from the study or, if the subject is continuing

to have clinical benefit, the Investigator may consult with the Sponsor's Medical Monitor or designee to allow the subject to remain in the study.

#### 4.2.2. Withdrawal Procedures

When a subject discontinues or is permanently withdrawn from the study, the Investigator will notify the Sponsor and ensure that the procedures listed in the 28 Day "Post-treatment Visit" column in the Schedule of Events (Table 15.2 and Table 15.3) are performed 28 ±7 days after the subject's last dose of study treatment and prior to initiating any new PVNS/GCT-TS therapy, including surgery.

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

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

If a subject discontinues study treatment before the end of Part 1, the end of Part 1 assessments (Part 1 Completion visit/Early Termination visit) should be performed at the time of early discontinuation (Table 15.2). These subjects will not be unblinded.

#### 4.2.3. Subject Replacement

Subjects withdrawn from the study will not be replaced.

### 4.3. Subject Re-screening Procedures

Re-screening is permitted for any candidate who failed to meet eligibility criteria upon initial screening. If rescreened, the candidate will not be given a new subject identification number. The initial screening information and the reason why the subject is ineligible for the initial evaluation will be recorded on the Screening Log. No data from the initial evaluation will be entered into the clinical database for a subject who is rescreened. However, MRI, ROM and surgical assessment may not need to be repeated, following consultation with Sponsor Medical Monitor.

# 5. TREATMENTS ADMINISTERED

## 5.1. Investigational Products

The study treatment, pexidartinib (PLX3397), is an HCl salt supplied in 200 mg-strength immediate-release capsules for oral administration.

The placebo capsules for this trial have an identical qualitative composition to the PLX3397 HCl capsules except no active pharmaceutical ingredient is included. The amount of mannitol is increased in the placebo blend to compensate for amount of active ingredient that is not added.

The placebo and pexidartinib capsules are identical in appearance to maintain the blind during Part 1.

## 5.2. Study Treatment Administration

Study treatment will only be given to randomized subjects under the supervision of the Principal Investigator or identified sub-Investigator(s). The study treatment for home administration during Part 1 will be dispensed to the subject for the first time at the P1-C1D1 visit (within 3 days of randomization), and the study treatment for home administration during Part 2 will be dispensed to the subject for the first time at the P2-C1D1 visit. Capsules should be swallowed and not crushed, chewed, or dissolved in liquid. In Part 1, subjects will receive either pexidartinib or matching placebo capsules. In Part 2, subjects will receive only pexidartinib capsules.

Study treatment administration will begin at the P1-C1D1 visit in the morning. At that visit, subjects will be instructed to take five capsules a day for the first 2 weeks; 1000 mg/d pexidartinib or matching placebo, this amount will be divided into a morning dose of two capsules and an evening dose of three capsules. After 2 weeks (at the P1-C1D15 visit), the dose will be reduced to two capsules in the morning and two capsules in the evening, 800 mg/d pexidartinib or matching placebo. Subjects who had a dose reduction during the first 2 weeks will continue treatment at their reduced dose. Doses should be taken in the fasting state (ie, no food for 1 hour before and 2 hours after dose administration). During the fasting period, subjects will be permitted to eat a low-fat snack (eg, crackers, toast, tea) if needed. Doses will be taken at approximately the same times of the day and approximately 12 hours apart. Each dosing cycle will be 28 days.

For the P1-C1D15 and P2-C1D15 visits and any visit when an ECG will be performed, subjects should be told to NOT take their morning dose of study treatment before coming to their study visit, which should be scheduled for the morning; instead, they should be told to bring their bottle of study treatment to the clinic and take their morning dose upon instruction by the study site. The time of dosing will be recorded. Subjects will then take their evening dose at home. If dose administered in the clinic is taken in the afternoon, then the subject should be instructed to skip their evening dose for that day.

For the P2-C1D1 visit (Week 25), subjects should be told to NOT take the morning dose of study treatment before their visit and to bring all unused capsules to the clinic for

accountability. Subjects who will continue into Part 2 will be given open-label pexidartinib for the first time at that visit, taking the same number of capsules per day as they were taking at the end of Part 1, ie, a maximum dose of 800 mg/d pexidartinib.

Between clinic visits, subjects will administer their study treatment at home and record the dosing information in the study dosing diary. Missed doses (those generally outside of a ± 2-hour dosing window) should be skipped and NOT administered as a double dose at the next dosing time point. Subjects who vomit their dose should be instructed NOT to make up that dose.

Further details on study treatment administration are contained in the separate Pharmacy Manual.

For subjects who undergo surgical resection of their tumor, study treatment will be discontinued before surgery and will not be restarted after surgery.

## 5.3. Dose Modification Guidelines

In both Parts 1 and 2, reducing or interrupting the dose for toxicity may take place at any time according to the guidelines in Table 5.1, Table 5.2 and Table 5.3. Dose reduction/interruption guidelines for hematologic and non-hematologic treatment-related TEAEs are based on severity. Dose interruptions can be implemented at the discretion of the treating physician to manage intolerable or clinically significant toxicity. If a dose interruption is required, study assessments should be performed as scheduled, irrespective of the study treatment delay, with the exception of PK assessments which should be deferred until treatment is resumed. Interruptions due to toxicity lasting >14 d require treatment discontinuation unless the medical monitor approves continuation.

When an odd number of capsules a day are to be taken, the larger number of capsules should be taken as the evening dose. For example, 600 mg/d or matching placebo = 3 capsules (1 capsule in the morning, 2 capsules in the evening). When an even number of capsules per day is to be taken, the morning and evening doses should be the same (eg, 800 mg/d or matching placebo = 4 capsules (2 capsules in the morning, 2 capsules in the evening) or 400 mg/d or matching placebo = 2 capsules (1 capsule in the morning, 1 capsule in the evening).

Dose reductions should be applied in increments of 200 mg/d or matching placebo (one capsule), with a maximum total reduction of 600 mg/d or matching placebo (ie, a minimum dose of 400 mg/d or matching placebo). Subjects unable to tolerate 400 mg/d or matching placebo (two capsules) will be discontinued. Once dose reduction takes place for toxicity, a dose re-escalation is generally not allowed unless approved after discussion with the Sponsor's Medical Monitor or designee.

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

**Table 5.1: Dose Modification Guidelines for Treatment-related Toxicities**

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

| Toxicity Grade (CTCAE v4), Frequency | When to Hold or Stop | When and How to Restart Dosing |
|---|---|---|
| 1st appearance | Interrupt until PLT $\geq 75 \times 10^9$/L | Reintroduce at the same dose. |
| 2nd appearance | Interrupt until PLT $\geq 75 \times 10^9$/L | If PLT does not recover to $\geq 75 \times 10^9$/L in $\leq 7$ days, reduce dose by 1 capsule. |
| 3rd appearance | Interrupt until PLT $\geq 75 \times 10^9$/L | Reduce dose by an additional capsule. |
| 4th appearance | Discontinue permanently | n/a |
| ■ Non-hematologic Grade 3[a] (excluding liver function test increases [see below]): start symptomatic treatment when possible | | |
| 1st appearance | Interrupt until resolved (Grade 0-1) | If recovered in < 5 days, resume at same dose. Reduce by 1 capsule if symptoms persist for ≥ 5 days despite supportive management. |
| 2nd appearance | Interrupt until resolved (Grade 0-1) | Reduce by an additional capsule. |
| 3rd appearance | Discontinue permanently | n/a |
| ■ Non-hematologic Grade 4 (excluding liver function test increases [see below]): start symptomatic treatment when possible | | |
| 1st appearance | Interrupt until resolved (Grade 0-1) | Reduce by 1 capsule. |
| 2nd appearance | Discontinue permanently | n/a |

ANC = absolute neutrophil count; CTCAE = Common Toxicity Criteria for Adverse Events; INR = international normalized ratio; n/a = not applicable; PLT = platelets; T = temperature; ULN = upper limit of normal

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

**Table 5.2: Dose Modification Guidelines for Liver Function Abnormalities**

| Toxicity Grade CTCAE v0.4 | Initial Action | Outcome | Action |
|---|---|---|---|
| ALT or AST Grade 2 (> 3-5 × ULN); No increase in bilirubin[a] | Re-check ALT and AST immediately<br>Hold study drug<br>Monitor weekly[b]<br>Check for changes to medications and for symptoms | Resolution to Grade 0-1 or baseline (no bilirubin increase) | Restart on resolution Grade 0-1 or baseline at 1 dose lower (reduce by one 200 mg capsule) |
| Grade 3 ALT or AST increase (> 5-20 × ULN); No increase in bilirubin[a] | Re-check ALT and AST immediately<br>Hold study drug<br>Monitor 2×/wk[b]<br>Check for changes to medications and for symptoms | Resolution to Grade 0-1 or baseline (no bilirubin increase) within 14 d | Restart on resolution to Grade 0-1 or baseline at 1 dose lower (reduce by one 200 mg capsule) |
| | | ALT and AST not decreasing within 14 d of holding study drug | Proceed to liver evaluation as outlined in Table 5.3. Restart only on resolution to Grade 0-1/baseline at 1 dose lower (reduce by one 200 mg capsule); For max AST or ALT > 8 × ULN, consult with medical monitor prior to re-start |
| Grade 4 ALT or AST (> 20 × ULN) | Discontinue treatment<br>Monitor 2×/wk until resolution to Grade 2<br>Follow-up until resolution Grade 0-1 or baseline<br>Check for changes to medications and for symptoms | All outcomes | Discontinue treatment; Proceed to liver evaluation as outlined in Table 5.3. If clear confirmed alternate cause, restart on resolution to Grade 0-1 or baseline at 1 dose lower (reduce by one 200 mg capsule) |
| Any grade ALT or AST increase[a] with any bilirubin increase or signs of hypersensitivity | Discontinue treatment<br>Monitor 2×/wk until resolution to Grade 2<br>Follow-up until resolution Grade 0-1 or baseline<br>Check for changes to medications and for symptoms | All outcomes | Discontinue treatment; Proceed to liver evaluation as outlined in Table 5.3. If clear confirmed alternate cause, restart on resolution to Grade 0-1 or baseline at 1 dose lower (reduce by one 200 mg capsule) |

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

[a]An increase in bilirubin is defined as all of the following: total bilirubin > ULN, total bilirubin > 20% above baseline, and direct bilirubin is > ULN. If all of these conditions are met, then bilirubin is considered increased and should be immediately re-checked. Pexidartinib treatment should be immediately discontinued for increased bilirubin unless and until there is a clear, confirmed alternate cause.
[b]If ALT, AST, or bilirubin worsens during the monitoring period, follow the applicable guidance for the worst toxicity grade.

**Table 5.3: Additional Liver Evaluation**

| Evaluation | Comments |
|---|---|
| Increase frequency of testing liver chemistries to twice per week, including INR, and continue until liver chemistries have stabilized, and then reduce to weekly until liver chemistries return to normal or baseline | Investigational treatment may be started after liver function tests recover to Grade 0 to 1 or baseline level, and in consultation with Medical Monitor |
| Detailed history focusing on medications and substances used: alcohol, change in medication dosages, new medications added, attention to use of acetaminophen, OTC medication use and recreational drug use. Check for change in diet or use of dietary supplements, with particular attention to dose and duration of any herbal product | Suspect medications will be discontinued or substituted for if possible |
| Detailed medical history and physical exam seeking new abnormalities | Evaluate abnormalities found |
| Full serological evaluation for hepatitis A, B, C and E (IgG and IgM). Check for autoimmune hepatitis with serological laboratory studies | If viral hepatitis or autoimmune hepatitis suggested, have subject evaluated by hepatologist |
| Liver ultrasound performed to evaluate liver and biliary tree | Evaluate any abnormalities found |
| Check history for exposure to chemical agents | Remove chemical exposure and have subject seen by hepatologist |
| Obtain hepatology consult if liver function continues to rise beyond 14 days | Contact Medical Monitor |
| **We request that cases be discussed with the Medical Monitor whenever investigational product is being held for liver function test abnormality.** | |

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

For suspected cases of cholestatic liver injury (eg, aminotransferase increase concurrent with hyperbilirubinemia, or liver biopsy suggesting cholestasis and/or ductopenia), patients will be followed to assess long-term outcome. Additional diagnostic and follow-up procedures might be implemented as appropriate to fully assess the event.

## 5.4. Concomitant Medications

During the study, if the use of any concomitant treatment becomes necessary (eg, for treatment of an AE), the treatment must be recorded on the source document and electronic Case Report Form (eCRF), including the reason for treatment, name of the drug, dosage, route, and date of administration. All medications including prescription, over-the-counter (OTC), herbal and other nutritional vitamins and/or supplements taken within 28 days of P1-C1D1 will be recorded on the eCRF. Analgesic use and analgesic regimen will be recorded as described in Section 6.4.11.

Subjects enrolled in studies with pexidartinib who are also receiving concomitant warfarin should have their anti-coagulation status carefully monitored, especially shortly after initiation of pexidartinib, for the potential need to make adjustments in warfarin dosing. In particular, INR should be obtained just prior to initiation of pexidartinib, within 1 to 2 weeks after initiation, and periodically thereafter. Dose adjustments of warfarin should be made as medically indicated.

Although pexidartinib does not appear to inhibit cytochrome P450 (CYP) drug-metabolizing enzymes to an important extent, caution is warranted when administering pexidartinib to subjects taking drugs that are highly dependent on CYP for metabolism and have a narrow therapeutic index. It is not known whether systemic exposure to these medications will increase while subjects are receiving pexidartinib.

Of the five major CYP isoforms, 3A4 (BFC) may be involved in Phase 1 metabolism of pexidartinib, with possibly CYP1A2 playing a minor role. Until information regarding exposure-toxicity and exposure-response relationships are available with pexidartinib, concomitant CYP3A4 inhibitors and inducers should be administered with caution, in the event they alter the systemic exposure to pexidartinib (see Section 15.1 for a list of common CYP3A4 inhibitors and inducers). In general, strong inhibitors or inducers of CYP3A4 should be avoided unless clinically necessary. These include anticonvulsants, certain mycin antimicrobials, and antiretrovirals. Some common examples include inhibitors such as erythromycin, clarithromycin, and inducers such as rifampicin, carbamazepine, phenytoin, efavirenz, and nevirapine.[21]

## 5.5. Precautions and Restrictions

Because pexidartinib is a substrate for CYP3A4/5 and some fruits are CYP3A4/5 inhibitors, foods or beverages containing CYP3A4/5 inhibiting fruits (eg, grapefruit, pomelo, star fruit, and pomegranate) should be avoided throughout the study.

## 5.6. Blinding and Unblinding

Part 1 will be the placebo-controlled double-blind phase of the study where treatment assignment will remain unknown to the study subjects, Investigators, study site personnel, safety laboratory personnel, central imaging readers, and representatives of Daiichi Sankyo involved in the conduct and/or management of the trial. Pexidartinib and placebo capsules will be identical in appearance. All study treatment (pexidartinib or placebo) will be labeled with the study number, a unique number, and any additional

information required in accordance with government regulations. Further details are contained in the separate Pharmacy Manual.

### 5.6.1. Unblinding

#### 5.6.1.1. Emergency Unblinding

In the cases of emergency where, in the Investigator's opinion, immediate unblinding of the treatment is necessary in order to evaluate further course of action, the Investigator should access the interactive web/voice response system (IXRS) to initiate subject unblinding as follows:

IXRS Option 04: **Emergency Unblinding**

What to enter for each subject:

- Confirm to continue with unblinding
- Subject ID

What the IXRS will provide back to the site:

- Subject's randomized treatment arm
- IXRS transaction confirmation

The Investigator may also contact the Sponsor's Medical Monitor or designee for information related to pexidartinib adverse effects in making the decision to unblind. (Contact information –refer to Section 10.1.2.) It is important to note that, once unblinded, a subject cannot receive further study treatment and must discontinue from the study.

The Investigator should promptly document and report to the Sponsor any unblinding for emergency reasons (eg, accidental unblinding, unblinding due to an SAE) of the investigational product(s).

The "Emergency Unblinding" option should not be used for subjects who may need unblinding to move into Part 2 after the confirmed disease progression in Part 1. Please see the next section for more information.

#### 5.6.1.2. Unblinding during Part 1 Week 13 to Week 25 for Disease Progression

In addition to the Emergency Unblinding option, if a central reading confirms RECIST 1.1-defined disease progression at or after Week 13 but before Week 25 visit, treatment assignment may be unblinded and potential continuation of a subject to Part 2 of the study will be assessed. If an investigator suspects disease progression during this period, an MRI should be submitted to the central reader with a request for an expedited read for potential disease progression. The investigator should alert the Sponsor and the Clinical Research Organization (Novella Clinical) Medical Monitors that the expedited read request has been made. Once the expedited read results are received, the investigator should discuss with the Sponsor and Novella Clinical Medical Monitors about the decision to unblind. If it is confirmed that the subject's study treatment should be unblinded, the Sponsor or designee will authorise the unblind in the IXRS system. Only

once the Sponsor authorisation has been logged in IXRS can the site then unblind the subject, which will also be done through IXRS:

IXRS Option 04: **Part 1 Week 13 Unblind**

What to enter for each subject:

- Confirm to continue with unblinding
- Subject ID

What the IXRS will provide back to the site:

- Subject's randomized treatment arm
- IXRS transaction confirmation

DO NOT USE THE EMERGENCY UNBLIND FUNCTION FOR SUBJECTS WITH DISEASE PROGRESSION as they will not be able to receive further treatment and must discontinue from the study (as Emergency Unblinding cannot be undone).

Once in receipt of the unblind information, the site may then choose to continue the subject into Part 2 of the study or discontinue the subject from the study. Subjects receiving placebo will be eligible for early entry into Part 2 of the study. Effective 30 Sep 2016, subjects receiving placebo will be discontinued instead of being eligible to enter Part 2. Subjects receiving pexidartinib will be discontinued from the study unless the Investigator and the Sponsor's Medical Monitor judge that the subject would potentially benefit from continued treatment with pexidartinib.

For statistical analysis of endpoints at the end of Part 1, a clinical data cut-off date will be defined for the point when all randomized subjects complete or are discontinued from Part 1 with appropriate End of Part 1 follow-up. All data up to this date will be cleaned and locked. Afterwards, unblinding of database will be performed to facilitate the data analyses, including the data from the double-blind Part 1 and available data from Part 2. Such unblinding is only intended for the sponsor and the Contract Research Organization. Subjects who entered Part 2 may continue to receive open-label pexidartinib treatment. Updated analysis of Part 2 data only, in the form of summary and descriptive statistics, will be performed at the end of the trial. Additional updates between the above-mentioned cut-off and end of the trial may also be performed.

#### 5.6.1.3. Unblinding at the End of Part 1

As of 30 Sep 2016, subjects on placebo in Part 1 are no longer allowed to enter Part 2 to receive open-label pexidartinib. After completion of the end of Part 1 assessments (Part 1 Completion visit/Early Termination visit), subjects who wish to continue onto the open label part of this study (Part 2) will be unblinded and those on placebo will be discontinued; subjects on pexidartinib in Part 1 may continue into Part 2 to continue to receive pexidartinib. (Detailed instructions will be provided separately.)

## 5.7. Description of Investigational Agents

**Pexidartinib (PLX3397)**

Pexidartinib is an HCl salt with a white to off-white crystalline solid appearance. PLX3397 HCl capsules are provided as 200 mg (200 mg free base equivalent) hypromellose capsules for oral administration containing the following excipients: Poloxamer 407, mannitol, crospovidone and magnesium stearate. Formulation of pexidartinib is J-3397-AF in hydroxypropyl methylcellulose capsules.

**Placebo**

The matching placebo capsules for oral administration contain Poloxamer 407, mannitol, crospovidone and magnesium stearate only, with an increased amount of mannitol to adjust for the absence of the active pharmaceutical ingredient.

## 5.8. Packaging and Labeling

PLX3397-HCl 200 mg capsules and placebo capsules are manufactured, packaged, and labeled according to Good Manufacturing Practices and Good Clinical Practices (GCP) at the following address:

Catalent Pharma Solutions, Inc.
10245 Hickman Mills Drive
Kansas City, MO 64137
USA

## 5.9. Storage, Handling, and Accountability

Study treatment (pexidartinib and placebo) in accordance with this protocol should be stored at the sites in a secure controlled facility and only provided to subjects who signed a consent form and are participating in the study. The study treatment must be stored at room temperature (do not store above 25ºC/77ºF). Excursions are permitted from 15ºC to 30ºC (59ºF to 86ºF), however approval for continued use must be obtained from Daiichi Sankyo for excursions <15 ºC or ≥25ºC (77ºF). Subjects will be instructed to store the study treatment at room temperature out of the reach of children or other cohabitants.

The Food and Drug Administration and other health authorities require accurate and up-to-date accounting of the disposition of all study treatment received by the site. Records of study treatment disposition required by federal law include the dates and quantities received from the Sponsor, the dates and quantities administered to a subject, including the identity of the subject, the dates and quantities returned by a subject (if applicable), and the dates and quantities of final disposition (ie, dates/quantities that unused study treatment is returned to the Sponsor/designee or dates/quantities that unused study treatment is destroyed on-site/off-site as applicable in accordance with GCP and site standard operating procedures). For any study treatment that is destroyed, destruction details must be documented on accountability and destruction logs and include at a minimum the number of bottles and capsules destroyed, batch number (if applicable), and the date and method of destruction. Any study treatment accidently or deliberately destroyed must be recorded in a timely fashion, including an explanation for the destruction in writing. Any discrepancies between the amounts of study treatment dispensed and returned must also be explained in writing.

The Investigator is responsible for the overall accountability and accurate and up-to-date documentation/disposition of all unused and used study treatment supplied by the Sponsor.

Dosage form (ie, capsules) site level accountability documentation is to be included with each drug supply return shipment (or other returning facility, such as another depot). This is required as part of the receiving records for return shipments.

Dosage form (ie, capsules) site level accountability documentation is required as part of the disposition records of IP. The dosage form site level accountability documentation should be appended to the Certificate of Destruction.

# 6. STUDY CONDUCT

## 6.1. Study Personnel and Organizations

The contact information for the Sponsor and Novella Clinical Medical Monitor for this study can be found in the Study Reference Manual. The contact information for the central imaging reader, central and any additional clinical laboratories, the coordinating Investigator for each member state/country, and Novella Clinical can be found in the Study Reference Manual. A full list of Investigators is available in the Sponsor's Investigator database.

## 6.2. Recruitment of Subjects

Subjects may be recruited from the Investigator's local practice or referrals from other physicians. Any advertisements used for recruitment purposes will be submitted to and reviewed by the IRB/IEC. It is not envisioned that prisoners or other populations who might be subject to coercion or exploitation will be enrolled into this study.

## 6.3. Treatment Group Assignments

Once all screening procedures have been completed and study eligibility has been confirmed, subjects will be enrolled in the study and centrally randomized in a 1:1 ratio to receive either pexidartinib or placebo twice daily for 24 weeks during Part 1 of the study. Randomization will be stratified by US versus non-US sites and by upper extremity versus lower extremity involvement. The randomization schedule will be developed by an independent third party vendor to ensure that the subject, site personnel, and Sponsor remain blinded to treatment assignment. Clinical site staff will obtain investigational medicinal product dispensing information by accessing the IXRS. See Study Reference Manual for further details.

After randomization, the first dose of study treatment (P1-C1D1) should occur within 3 days of the randomization date.

During Part 2 of the study, all subjects will receive open-label pexidartinib.

## 6.4. Study Procedures

Study procedures are summarized in Table 15.2 and Table 15.3. Descriptions of the specific study procedures are provided in the following subsections, and study procedures are listed by visit in Section 15.2. Additional details are provided in the Study Reference Manual, MRI Procedure Manual, or Laboratory Manual as applicable.

Each subject must sign and date an informed consent form before undergoing any study procedure (including screening procedures, unless the screening procedure as outlined in the Study Reference Manual and is considered standard of care). New safety measures were implemented effective on 30 Sept 2016 (see Section 1.6). Investigators and subjects must be informed of the new safety information and decide whether to continue in the

study. If, after consultation with the subject, it is deemed to be in their best interest to continue treatment, the subject must be re-consented.

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

If a dose interruption is required, study assessments should be performed as scheduled, irrespective of the study treatment delay, with the exception of PK assessments which should be deferred until the first clinical visit after dosing resumed.

The last subject last visit defines the end of the study.

All subjects who complete at least 24 weeks of open-label pexidartinib treatment in Part 2 without disease progression will be eligible to continue for longer efficacy and safety follow-up or to participate in a separate protocol to continue receiving pexidartinib.

### 6.4.1. Demographics and Medical History

Subject demographic data such as age, sex, ethnicity (where legally allowed), and race will be obtained during the Screening visit. A complete medical history will also be obtained during the Screening visit. The medical history will comprise all prior and current medical history, including PVNS/GCT-TS treatment history and smoking history.

### 6.4.2. Vital Signs and Subject Weight

Vital signs, including systolic/diastolic blood pressure, pulse rate and temperature will be measured in accordance with institutional standards and generally should be performed before invasive procedures, eg, blood draws. Vital signs and weight will be measured at the indicated study visits in the Schedule of Events.

Height will be measured at the Screening visit only.

### 6.4.3. Physical Examination

A physical examination will include the following systems or areas: general appearance; oral cavity and neck; cardiothoracic; dermatologic; abdominal; musculoskeletal; and neurological. The examination will be performed by a qualified individual such as the Investigator at the study visits indicated in the Schedule of Events (Table 15.2 and Table 15.3).

### 6.4.4. Range of Motion Assessment

Range of motion of the joint will be assessed by a qualified, independent, and blinded third party, such as an orthopedic surgeon or a physical therapist, using goniometers according to a standardized method based on American Medical Association disability criteria.[20] Measurements will be recorded in degrees. Details of the measurement procedure for each joint will be provided in the Study Reference Manual.

### 6.4.5. Electrocardiogram

A standard 12-lead ECG will be obtained at the study visits indicated in the Schedule of Events (Table 15.2 and Table 15.3). Subjects should rest in the supine position for at least

5 minutes before the ECG recording is started. The ECG recordings must be performed using a standard high-quality and high-fidelity electrocardiography machine equipped with computer-based interval measurements. For safety monitoring purposes, the ECGs should be reviewed, signed, and dated promptly by a qualified physician (or physician's assistant, nurse practitioner) and any clinically important finding recorded on the appropriate eCRF. The Investigator is responsible for interpreting all ECGs. The results may include heart rate, RR interval, PR interval, QRS interval, QT interval, and QTcF interval.

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

### 6.4.6. Echocardiogram

A resting echocardiogram (ECHO) or multi-gated acquisition (MUGA) scan will be performed at the study visits indicated in the Schedule of Events for Part 1 (Table 15.2) and Part 2 (Table 15.3) of the study to evaluate subjects' cardiac function throughout study participation. (For the purposes of this protocol, "ECHO scan" and "MUGA scan" will be used interchangeably.) The choice of whether to perform ECHO or MUGA scanning will be based on the preference of the Principal Investigator, but *platforms should not be switched* during the course of a subject's study participation. Echocardiogram or MUGA scanning should only be repeated if more than 3 months have elapsed since the last procedure. Subjects who show a reduced ejection fraction relative to baseline at the last visit should be followed until a stable ejection fraction is measured by two consecutive tests. For safety monitoring purposes, the scan must be evaluated promptly by a qualified physician (or qualified physician's assistant or nurse practitioner). Clinically important findings, including the ejection fraction, will be recorded on the appropriate eCRF. The Investigator is responsible for providing the interpretation of all scan findings.

### 6.4.7. Clinical Laboratory Evaluations

Clinical laboratory evaluations will be performed centrally at the study visits indicated in the Schedule of Events (Table 15.2 and Table 15.3). Collection, processing, labeling, handling, and shipment of samples will be outlined in the separate Laboratory Manual. Local laboratory evaluations are permitted to facilitate assessment of AEs or support dosing decisions; every effort should be taken to submit a sample to the central laboratory at the same time for unscheduled samples.

Clinical laboratory evaluations will be performed as outlined below:

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

**Clinical Chemistry**

- Sodium
- Total protein

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

* Fasting is recommended but not required.

**Liver Function Tests**

**Alkaline phosphatase**

- AST
- ALT

**Total bilirubin**

- Direct bilirubin
- GGT

**Hematology**

**Red blood cell count**

- White blood cell count with differential
- Platelet count

**Hemoglobin**

- Hematocrit

**Hepatitis Panel**

Hepatitis B virus surface antigen test and HCV antibody test

**Coagulation**

Prothrombin time, activated partial thromboplastin time, and INR.

**Hormone Tests**

**Females**

- FSH
- LH
- Progesterone

**Males**

- FSH
- LH
- Testosterone

**Females** **Males**

- Estradiol

**Urinalysis (dipstick and microscopic analysis)**

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

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

### 6.4.8. Patient Reported Outcome Instruments

Subjects will complete via an electronic diary the BPI Worst Pain NRS item, the Worst Stiffness NRS item, the PROMIS Physical Function Scale, the EQ-5D-5L, and the Patient Global Rating of Concept item for ability to carry out everyday activities at the indicated study visits in the Schedule of Events (Table 15.2 and Table 15.3). In addition, subjects will be given both the BPI Worst Pain NRS item and the Worst Stiffness NRS item to complete on an outpatient basis, for at least 4 of 7 consecutive days (Day -7 to Day -1) prior to the indicated study visits in the Schedule of Events. At the Week 25 visit, subjects will also complete the Patient Global Impression of Change item for tumor-related stiffness.

On study visit days including Screening, subjects will complete instruments prior to any invasive procedures and prior to the morning dose.

#### 6.4.8.1. Most Disturbing Symptom Assessment

Before initiating study treatment, the subject will be asked to identify which symptom of pain, stiffness, or compromised ability to carry out everyday activities they find to be most disturbing.

#### 6.4.8.2. BPI Worst Pain NRS Item

The BPI Worst Pain NRS item is a one-item self-administered questionnaire assessing the “worst” pain in the last 24 hours (Section 15.5). The NRS for this item ranges from 0 (“no pain”) to 10 (“pain as bad as you can imagine”).

#### 6.4.8.3. Worst Stiffness NRS item

The Worst Stiffness NRS item is a one-item self-administered questionnaire assessing the “worst” stiffness in the last 24 hours (Section 15.6). The NRS for this item ranges from 0 (“no stiffness”) to 10 (“stiffness as bad as you can imagine”).

#### 6.4.8.4. PROMIS Physical Function Scale

Physical function items relevant to the assessment of lower and upper limb function are to be selected from the PROMIS physical function item bank (Section 15.7). Items assessing lower limb function will be administered to subjects with the lower extremity tumors, and items assessing upper limb function will be administered to subjects with upper extremity tumors. The results from both sets of items will be combined and analyzed together.

#### 6.4.8.5. EQ-5D-5L

The EQ-5D-5L is a preference-based general health status or health-related quality of life instrument consisting of two parts (Section 15.8). The first part comprises five domains (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) each of which can have five levels ranging from no problems through profound difficulties. Accordingly, 3125 potential health profiles can be generated to which public preferences or utilities are applied. These data can subsequently be used in an economic evaluation or cost-utility analysis. The second part of the EQ-5D-5L is a Visual Analogue Scale on which the subject rates their current health, with 0 representing the "worst health you can imagine" and 100 representing the "best health you can imagine."

#### 6.4.8.6. Patient Global Impression of Change and Global Rating of Concept Items

A Patient Global Impression of Change item (Section 15.9) assessing tumor-related stiffness will be administered at the Part 1 Completion (Week 25) and 28 Day Post-treatment visits. A Patient Global Rating of Concept item (Section 15.9) for ability to carry out every day physical activities will be administered at defined study visits. Results from these items will be used in exploratory analyses to define the magnitude of meaningful change on the Worst Stiffness NRS and PROMIS Physical Function Scale, respectively.

### 6.4.9. Tumor Imaging

Non-contrast MRI of the affected joint will be performed at the study visits indicated in the Schedule of Events (Table 15.2 and Table 15.3). All MRI scans will be centrally read. Local evaluation of radiological response, stable or progressive disease according to RECIST 1.1 will be recorded in the eCRF. The central MRI assessment report of progression status will not be provided unless requested. The Investigator will follow procedures (including instructions on proper imaging technique, and labeling) outlined in a separate MRI Procedure Manual. The results of the baseline, centrally read MRI scan will be used to qualify a subject, and all subsequent MRI scans will be read centrally in a manner blinded to treatment assignment and other clinical trial data at the conclusion of Part 1, the placebo-controlled portion of the study.

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

unblinded, and subjects receiving placebo will be eligible for early entry into Part 2 of the study as described in the Study Reference Manual. Effective 30 Sep 2016, subjects receiving placebo will be discontinued instead of being eligible to enter Part 2. Subjects receiving pexidartinib will be discontinued from the study unless the Investigator and the Sponsor's Medical Monitor judge that the subject would potentially benefit from continued treatment with pexidartinib.

During Part 2, if indicated, Investigators should request confirmation of radiologic disease progression by central read. Otherwise, central reading of MRI scans may be performed during or after the subject has completed the study. Details for Part 2 MRI scan reads are outlined in the MRI Procedure Manual.

Subjects who terminate the study because of radiologic disease progression will not have a follow-up MRI at their Post-treatment visit.

### 6.4.10. Surgical Assessment Questionnaire

The Surgical Assessment Questionnaire (Section 15.10) will be completed by a qualified individual (eg, orthopaedic oncologist) to assess the surgical status of the subject at the Screening visit and at time points shown in the Schedule of Events.

### 6.4.11. Surgical Data and Outcome Follow-up

At or after Week 25 evaluation, subjects may be considered for surgery to remove the tumor. The surgery is recommended to be performed 1-3 weeks after the last dose of the study treatment. After completion of the end of Part 1 assessments (Part 1 Completion visit/Early Termination visit), subjects who wish to continue onto the open label part of this study (Part 2) will be unblinded and those on placebo will be discontinued and will not need to have surgical data follow-up.

Detailed information about the surgery will be collected, including but not limited to:

- Reasons of the surgery
- Planned surgical procedure and actual surgical procedure performed
- Surgical margin
- Copies of surgical report and pathology report, if available
- Surgery complications such as infection, delayed healing

Surgically resected tumor samples will be collected for evaluation of study treatment effects on tumor cells.

Before the surgery is performed, the subject should have an additional visit for ROM and PRO (pain and stiffness scores, PROMIS questionnaire) evaluation, if these are not done within 6 weeks prior to the surgery. Subjects do not need to have the End-of-Study visit if a decision has been made to have surgical resection of the tumor under study treatment.

At 4 months (+/- 2 weeks) after the surgery, the subject should have a visit for MRI scan of the tumor affected joint, ROM and PRO (pain and stiffness scores, PROMIS questionnaire) evaluations. After this visit, the subject should be followed for disease

recurrence (defined as the need for any new therapeutic intervention of TGCT) at 8, 12, 18 and 24 months after surgery. Such follow-up can be performed via phone contact with the subject.

Subjects who undergo surgery may be rolled into a separate protocol for surgery and its outcome data collection.

### 6.4.12. Analgesic Use and Analgesic Regimen

Subjects will have an electronic diary in which to record any analgesics, including nonsteroidal anti-inflammatory drugs and prescription analgesics, taken during the period before investigational product initiation and during the time period when the BPI Worst Pain and Worst stiffness Items are scheduled for completion. Subjects must have a stable prescribed analgesic regimen during the 2 weeks prior to the first dose of study treatment. During the study, whenever possible, the type and dose of long-acting narcotic analgesic and non-narcotic analgesic should be kept stable while the dose of short-acting (or rescue) narcotic analgesic might be titrated as needed. Analgesic use will be quantified by multiplying the daily dose unit by the number of units taken, averaged by the number of days with available data.[22] For subjects who have changed narcotic type or if dosages have been changed in subjects concomitantly receiving different narcotic types, analgesic use will be calculated following equianalgesic conversion to morphine-equivalent doses.[23]

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

### 6.4.13. Healthcare Resource Use and Productivity

During Part 1, major HCRU-and subject productivity (Section 15.12) will be recorded at baseline, selected clinic visits, and at the Completion and 28 Day Post-treatment visits (Table 15.2). Questions will be administered to the subject as part of the clinical interview.

Information will be captured about episodes of hospitalization, including date of admission, date of discharge, primary diagnosis at discharge, and days of different levels in inpatient intensity of care (Section 15.12). Information on subject employment status will be recorded and, if the subject is working, days lost from work because of PVNS/GCT-TS will be assessed (Section 15.11).

### 6.4.14. Pregnancy Test

For female subjects of child-bearing potential only, a serum pregnancy test (β-human chorionic gonadotropin) will be performed at the study visits (centrally for all but local laboratory is allowed at the end of study visit) indicated in the Schedule of Events (Table 15.2 and Table 15.3).

### 6.4.15. Pharmacodynamic Sampling

Archival surgical tissue from PVNS/GCT-TS tumors (if available) will be obtained at the Screening visit (or when available and consented) and will be collected and stored for

exploratory biomarkers related to pexidartinib and/or disease. Plasma for circulating PDy biomarkers will be collected once per day on the same days when PK blood sample(s) are drawn (eg, predose) and will be analyzed for markers of pexidartinib exposure and for exploratory biomarkers, including CSF-1 and adiponectin.

Consult the Laboratory Manual for detailed instructions on collection, processing, handling, storage, and sample shipment.

### 6.4.16. Pharmacokinetic (PK) Sampling

PK sampling will be performed at the study visits indicated in the Schedule of Events for Part 1 (Table 15.2) and Part 2 (Table 15.3). Each site must choose one of the schedules for each subject and must adhere to the selected schedule (Table 6.1) for the duration of the study:

**Table 6.1: PK Schedules**

| Visit | Schedule 1 | Schedule 2 |
|---|---|---|
| Week1 P1C1D1 | Pre-dose | Pre-dose |
| Week3 P1C1D15 | Pre-dose<br>Post-dose: 0.5, 1, 2, 3, 4, and 6 hours | Pre-dose<br>Post-dose: Between 1-3 hours |
| Week5 P1C2D1 | | Random post-dose |
| Week9 P1C3D1 | Random post-dose | Random post-dose |
| Week17 P1C5D1 | Random post-dose | Random post-dose |
| Week25 P2C1D1 | Pre-dose | Pre-dose |
| Week27 P2C1D15 | Pre-dose<br>Post-dose: 0.5, 1, 2, 3, 4, and 6 hours | Pre-dose<br>Post-dose: Between 1-3 hours |
| Week29 P2C2D1 | | Random post-dose |

Subjects should be told to NOT take the morning dose of study treatment at the P1-C1D15, P2-C1D1 (Week 25), and P2-C1D15 visits. Instead, they should be told to bring their bottle of study treatment to the clinic and follow dosing instruction by the site staff.

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

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

### 6.4.17. Adverse Events

Adverse events will be monitored throughout the study. Adverse events and SAEs will be monitored and recorded in the source documents and eCRFs from the time the subject signs informed consent through the subject's Post-Treatment Visit 28 days (± 7 days)

after the last dose of study treatment. Adverse events (including clinically significant changes in laboratory results, ECHO results, and hormone testing results) should be monitored until they are resolved or are determined to be due to a subject's stable or chronic condition or intercurrent illness(es). If an AE remains unresolved at the conclusion of the study, the Investigator should follow the AE until s/he deems it to be resolved, stable, or not expected to worsen per medical judgment (eg, resolved with sequelae). Definitions, documentation, and reporting of AEs are described in detail in Section 9.

### 6.4.18. Study Treatment Compliance

At the study visits indicated in the Schedule of Events, blinded pexidartinib or placebo will be dispensed to subjects in Part 1, and open-label pexidartinib will be dispensed to subjects in Part 2. The appropriate study personnel will document and maintain records of study treatment dispensing to each subject and any returns at each study visit.

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

At each clinic visit, subjects will be assessed for compliance with study treatment administration, ie, actual capsules taken / expected capsules taken; so must return all bottles (used/unused) at each dispensing visit.

Further details can be found in the Study Reference Manual.

## 6.5. Study Procedures

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

A deviation to any protocol procedure, or a waiver to any stated criteria will not be allowed in this study except where necessary to eliminate immediate hazard(s) to the subject. Sponsor must be notified of all intended or unintended deviations to the protocol (eg, inclusion/exclusion criteria, dosing, missed study visits) on an expedited basis.

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

If a subject was ineligible or received the incorrect dose or investigational treatment and had at least one administration of the study treatment, data should be collected for safety purposes, and the Sponsor's Medical Monitor or designee should be informed immediately.

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

# 7. STATISTICAL METHODS

## 7.1. Randomization and Stratification

The randomization ratio for Part 1 of the study will be 1:1 for active (pexidartinib) versus placebo. Randomization will be stratified by US versus non-US sites and by upper extremity versus lower extremity involvement.

## 7.2. Analysis Sets

Randomized Analysis Set

The Randomized Analysis Set consists of all subjects in this study that were randomized.

ITT Analysis Set

The Intent-to-treat (ITT) Analysis Set is defined as all randomized subjects, which is the same as the Randomized Analysis Set. The primary efficacy analysis as well as all other efficacy analyses will be performed in the ITT Analysis Set. Subjects will be included in the treatment group to which they were randomized, regardless of the treatment actually received.

Safety Analysis Set

The Safety Analysis Set consists of all subjects in the Randomized Analysis Set who received at least one dose of study treatment. All safety analyses will be completed in the Safety Analysis Set. Subjects will be included in the treatment group based on the actual treatment they received.

Per-protocol Analysis Set

The Per-protocol Analysis Set will be defined as subjects in the ITT Analysis Set who did not have major eligibility/protocol violations and who are compliant with regard to study treatment administration, defined as taking at least 70% of their scheduled dose of study treatment, regardless of scheduled dose reduction.

## 7.3. Procedures for Handling Missing, Unused, and Spurious Data

For the primary efficacy analysis as well as for all analyses of responder proportion endpoints performed on the ITT and Per-protocol Analysis Sets, subjects who do not provide data for the responder endpoint will be considered nonresponders, ie, assigned to the less favorable outcome for the endpoint. Subjects who discontinue the study before Week 25 and do not have a Week 25 MRI will be considered nonresponders. Analysis of the endpoints involving range of motion and PROs, which are measured at multiple time points, by comparing the central tendency of continuous variables between treatment groups (not the responder type of analysis for a binary variable), will be performed using mixed models for repeated measurements (MMRM) incorporating all available measurements from each subject.[24,25,26,27,28]

## 7.4. General Statistical Considerations

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

In general, the baseline value for an efficacy variable, including that for a PRO variable, is the last non-missing value before randomization. The baseline value for a safety variable is the last non-missing value before the first dose of study treatment. The exceptions are several special variables in Part 2, such as the tumor response and duration of response variables evaluated for pexidartinib treatment for subjects randomized to placebo in Part 1; in such cases, the baseline for Part 2 is defined as the last non-missing value before the first dose in Part 2. Further details are contained in the following sections and in the Statistical Analysis Plan (SAP).

For the primary efficacy endpoint and secondary efficacy endpoints with the exception of duration of response, treatment comparison at Week 25 will be performed based on the data collected during the visits between baseline and Week 25. Point estimate and accompanying 95% confidence interval (CI) will be computed. For duration of response, Kaplan-Meier product limit methodology will be utilized to provide estimates, including those for the median and 25th and 75th percentiles.

All statistical tests will be 2-sided. Unless otherwise specified, all tests will be carried out at the alpha = 0.05 level of significance.

## 7.5. Study Population Data

Subject disposition will be summarized for each randomized treatment group and in total for the ITT Analysis Set. The total number of subjects for each defined analysis population will also be tabulated. The demographic and baseline characteristics will be summarized descriptively for the ITT, Per-protocol, and Safety Analysis Sets. Study treatment exposure and study duration will be summarized using descriptive statistics by treatment group for the Safety Analysis Set.

## 7.6. Efficacy Analyses

### 7.6.1. Primary Efficacy Analysis

The primary efficacy endpoint is the proportion of subjects who achieve a CR or PR at the Week 25 Visit (Table 2.1) based on centrally read MRI scans and RECIST 1.1. The primary analysis will be completed using the ITT Analysis Set. The proportions in the two treatment groups will be compared using Fisher's exact test (two-sided) at the alpha = 0.05 level of significance. In addition, the two-sided 95% CI for the difference between the responder proportions in the two treatment groups will be provided, using the Wilson method.[29, 30]

As a supportive analysis, mid-p adjustment of Fisher's exact test will also be performed.[31,32]

Additionally, as a sensitivity analysis, the Cochran-Mantel-Haenszel test will also be carried out with the strata of US and non-US sites.

### 7.6.2. Secondary Efficacy Analyses

Secondary efficacy analyses will include the following treatment comparisons at the Week 25 visit using the ITT Analysis Set:

1. Mean change from baseline in range of motion of the affected joint, relative to a reference standard for the same joint (as defined below).[20]
2. Proportion of responders based on centrally evaluated MRI scans and TVS.
3. Mean change from baseline score in the PROMIS Physical Function Scale.
4. Mean change from baseline score in the Worst Stiffness NRS item.
5. Proportion of responders based on BPI Worst Pain NRS item and analgesic use (BPI-30, as defined below).

The above-listed endpoints will be analyzed using a hierarchical ("gatekeeping") testing procedure.[33] Thus, if the primary analysis of responder rate by RECIST 1.1 is statistically significant favoring pexidartinib ($p < 0.05$), then secondary endpoint #1 will be analyzed, also based on the use of a two-sided test at the alpha = 0.05 level of significance. If secondary endpoint #1 is statistically significant ($p < 0.05$), then the testing procedure will proceed to secondary endpoint #2, and so on. If the test for a particular endpoint is not statistically significant, the inference for all subsequent endpoints in the hierarchy will not be performed.

For responder analysis based on the BPI Worst Pain NRS item and analgesic use, a BPI-30 responder will be defined as a subject who (i) experienced a decrease of at least 30% in the mean BPI Worst Pain NRS item and (ii) did not experience a 30% or greater increase in narcotic analgesic use, comparing data collected during a 7-day period prior to the current visit for responder assessment with baseline values collected prior to the first dose of study treatment. A decrease of at least 30% in BPI Worst Pain NRS item has been shown to be clinically meaningful in several therapeutic areas.[34, 35] Subjects who do not provide data for the endpoint will be considered to be non-responders. Definition for increase in analgesic use is outlined in Section 6.4.11. See SAP for further details.

The proportion of TVS responders (ie, those who achieve a CR or PR based on TVS criteria) at the Week 25 (Part 1 Completion) visit will be analyzed using the same methodology as that used for the primary efficacy endpoint (Section 7.6.1).

Other secondary endpoints will be analyzed using MMRM. The dependent variable will be the change from baseline. Each of these models will include fixed effects for treatment group, time point, treatment group-by-time interaction, stratification factor of US sites versus non-US sites, and the baseline value of the corresponding endpoint as well as the baseline-by-time interaction. An unstructured variance-covariance matrix will be used. Statistical comparisons between treatment groups will be made at the specified time point.

For the endpoint of range-of-motion, raw measurements of the affected joint will be performed using a goniometer and expressed in degrees (Section 6.4.4). The value for a given joint will be normalized to a reference standard, ie, full range-of-motion for the same joint, to provide a relative value. The reference standard will be derived from American Medical Association disability criteria [20] and are included in the SAP. The change from baseline in relative range-of-motion at the Week 13 and Week 25 visits will then be calculated. MMRM will be employed to analyze the change from baseline, and a statistical comparison between treatment groups will be made for the Week 25 visit. Joint type will also be properly accounted for in the model.

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

Duration of response will be summarized for responders in each of the following three groups:

(A) Subjects randomized to receive pexidartinib in Part 1 using data from Part 1 and Part 2;

(B) Subjects randomized to receive placebo in Part 1;

(C) Subjects in Part 2 who were randomized to receive placebo in Part 1.

For Group A, tumor assessment data from both Part 1 and Part 2 will be combined, and the baseline assessment will be the one recorded at the Screening visit. For Group B, the duration of response will be censored at Week 25 visit if no disease progression was documented, with the screening assessment serving as baseline. For Group C, the tumor assessment data in Part 2 will be used, with the baseline assessment being the last one before the first dose of pexidartinib in Part 2.

For each of the above three groups, the percentage and 95% CI will be provided for the best overall response in the order of CR, PR, SD, PD, and “Inevaluable.”

The analyses for the primary efficacy endpoint and BPI Worst Pain NRS item associated endpoints will also be performed on the Per-protocol Analysis Set as a sensitivity analysis.

### 7.6.3. Additional Efficacy Analyses

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

- Proportion of responders on the BPI Worst Pain NRS item and analgesic use by BPI-2p definition (see below)

- Proportion of responders on the BPI Worst Pain NRS item and analgesic use by BPI-50 (see below)
- Proportion of responders on the Worst Stiffness NRS item
- Proportion of responders on the PROMIS Physical Function Scale
- Mean change from baseline in the BPI Worst Pain NRS item
- Patient Global Impression of Change item for tumor-related stiffness and Patient Global Rating of Concept item for ability to carry out every day physical activities.
- Duration of BPI-based symptom response, analyzed for BPI-30, BPI-50 and BPI-2p.
- Results of the Surgical Assessment Questionnaire in Part 1.
- Response based on the change in the SSD of the tumor on MRI, referred to as "modified RECIST 1.1–SSD"
- Amount of joint/tissue damage (eg, bone erosion, bone edema, cartilage loss) assessed on MRI based on adaptations of the RAMRIS and WORMS
- Analgesic use expressed as morphine-equivalent doses in Part 1[22]
- EQ-5D-5L parameters in Part 1
- Major HCRU and productivity in Part 1
- Duration of response based on MRI and modified RECIST 1.1-SSD
- Response based on the most disturbing symptom of pain, stiffness, or compromised ability to carry out everyday activities.
- Proportion of subjects receiving surgical resection of their tumor by 25 weeks, 49 weeks, 73 weeks, and 97 weeks of pexidartinib treatment

For responder analysis based on the BPI Worst Pain NRS item and analgesic use, a BPI-2p responder will be defined as a subject who (i) experienced a decrease of at least 2 points in the mean BPI Worst Pain NRS item and (ii) did not experience a 30% or greater increase in narcotic analgesic use, comparing data collected during a 7-day period prior to the current visit for responder assessment with baseline values collected prior to the first dose of study treatment. A BPI-50 will have the same definition except the subject must experience a decrease of at least 50% in the mean BPI Worst Pain NRS item. Subjects who do not provide data for the endpoint will be considered to be non-responders. Definition for increase in analgesic use is outlined in Section 6.4.11. See SAP for further details.

The endpoints involving the PRO assessments, amount of joint/tissue damage, response based on MRI and modified RECIST 1.1-SSD, and duration of response will be analyzed using the same methods as those used for the primary and secondary endpoints.

Duration of BPI symptom response for a responder is the interval from the first time BPI symptom response is documented to the first subsequent time point when the BPI

symptom response is not met. The definition applies to BPI symptom response of BPI-30, BPI-50 and BPI-2p. Duration of BPI symptom response will be summarized in a way similar to that for duration of tumor response by RECIST 1.1.

For subjects who undergo surgical resection, the surgery-related data will be listed, including those collected in the separate protocol, if applicable. Proportion of subjects receiving surgical resection of their tumor by 25 weeks of pexidartinib treatment will be calculated regardless of whether blinded or open-label pexidartinib treatment, or both, was taken. The numerator is the number of subjects having the surgical resection of the tumor within 36 weeks of the first treatment of pexidartinib, taking into account the 12 weeks allowable window. The denominator is the number of subjects who complete at least 24 weeks of pexidartinib treatment. Likewise, the proportion of subjects receiving surgical resection of their tumor by 49 weeks, 73 weeks, and 97 weeks of pexidartinib treatment will be calculated similarly.

### 7.6.4. Subgroup Analyses

The primary endpoint and BPI Worst Pain NRS item will be also analyzed in the following subgroups of the ITT population:

- Subjects with disease located in large joints (shoulder, elbow, hip, or knee);
- Subjects with disease located in small joints (joints other than the shoulder, elbow, hip, or knee);
- Subjects with disease located in the knee;
- Subjects with GCT-TS type of TGCT;
- Subjects with PVNS type of TGCT;
- Subjects with lower extremity tumors;
- Subjects with upper extremity tumors;
- Subjects at US sites;
- Subjects at sites outside of the US;
- Subjects at sites in the EU region only.

In each subgroup defined above, the analysis will be carried out using the same type of methodology as described for the overall analysis of the corresponding endpoint. These results will be considered exploratory because of the multiplicity issue and also smaller sample sizes that cannot be pre-specified. For subgroups without an adequate number of subjects, the analysis will not be performed.

## 7.7. Pharmacodynamics/Biomarkers

Blood samples collected at specified time points will be analyzed for markers of pexidartinib exposure and for exploratory biomarkers, including CSF-1 and adiponectin.

Available and consented archival tissue specimens from PVNS/GCT-TS tumors will be collected and stored for exploratory biomarkers related to pexidartinib and/or disease.

Plasma will be analyzed for markers of pexidartinib exposure and for exploratory biomarkers, including CSF-1 and adiponectin. No formal statistical analysis of PDy endpoints will be performed. Pharmacodynamic data from each assay will be listed and possible relationships between PK and PDy variables may be explored. Any biological activity will be described.

Biomarker data will be summarized using descriptive statistics by treatment and visit. Exposure-biomarker data will be analyzed graphically and may be modeled if data permit.

## 7.8. Pharmacogenomic Analysis

### 7.8.1. Genomic or Genetic Banking and Analysis

A single blood sample (10 mL) for pharmacogenomics analysis will be collected from each subject who consent to this test. Pharmacogenomic sample may also be collected from discontinued subjects who provide consent. Participation in this part of the study is optional for all subjects.

The following procedures will be used for the long-term preservation (banking) of DNA specimens extracted from subjects' blood samples. Pharmacogenomic samples may be analyzed for genes involved in absorption, distribution, metabolism, elimination, safety, and efficacy of pexidartinib. Additionally, samples may be analyzed for genes involved in pexidartinib related signaling pathways, or to examine diseases or physiologic processes related to pexidartinib. DNA samples will not be immortalized or sold to anyone. This information may be useful in increasing the knowledge of differences among individuals in the way they respond to the study drug, as well as helping in the development of new drugs or improvement of existing drugs.

Specimen shipping and handling details will be included in the laboratory manual.

#### 7.8.1.1. Disclosure of the Results of Genomic or Genetic Analysis

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

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

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

If the subject withdraws consent, the banked blood samples will be properly and promptly disposed of. However, the data will not be discarded if genetic analysis has been completed before the subject withdraws consent.

## 7.9. Pharmacokinetics and Exposure–Response Analyses

Plasma–concentration time data for pexidartinib will be summarized by visit and time using descriptive statistics. Plasma–concentration data from these samples will be analyzed using a PopPK approach using nonlinear mixed effects modeling. Data from

Phase 1 studies will be used to inform and stabilize the structural PK model and will be pooled with Phase 3 data to assess and characterize the inter- and intra-subject variability in PK and to identify significant covariates. PK parameters will include apparent clearance and volume of distribution along with transfer rate constants such as absorption and elimination rates. Additionally, based on post hoc Bayesian methods, estimates of exposure such as $C_{max}$, $C_{trough}$, $C_{av}$ and $AUC_{ss}$ may also be reported.

Exposure–Response

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

## 7.10. Safety Analysis

The analyses of safety will be performed on the Safety Analysis Set. The summary and display of TEAEs will be performed for the following data sets:

(i) Part 1 data for the subjects who received blinded pexidartinib in Part 1;

(ii) Part 1 data for the subjects who received blinded placebo in Part 1;

(iii) All data from open-label pexidartinib treatment, ie, Part 2 data from all subjects;

(iv) Aggregate pexidartinib data, ie, data from Parts 1 and 2 for the subjects who received pexidartinib in Parts 1 and 2 plus Part 2 data for the subjects who received blinded placebo in Part 1.

Terminology from version 19.1 of the Medical Dictionary for Drug Regulatory Activities (MedDRA) will be used to assign System Organ Class (SOC) and preferred term (PT) classification to AEs and diseases, based on the original terms entered on the eCRF.

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

### 7.10.1. Analysis of Treatment-emergent Adverse Events

TEAEs are AEs that occur, having been absent before the first dose of study treatment, or have worsened in severity after the initiating the study treatment. TEAEs will be coded using MedDRA and assigned grades based on version 4.0 of the National Cancer Institute's Common Terminology Criteria for Adverse Events (NCI CTCAE). The number and percentage of subjects reporting TEAEs will be tabulated by the worst CTCAE grade, SOC, and PT, with a breakdown by data set (Section 7.10). Similarly, the number and percentage of subjects reporting treatment-emergent SAEs will be tabulated, as well as TEAEs leading to discontinuation of study treatments.

A by-subject AE (including treatment-emergent) data listing including but not limited to verbatim term, preferred term, system organ class, CTCAE grade, and relationship to

study treatment will be provided. Deaths, other SAEs, and other significant AEs, including those leading to discontinuation of study treatments, will be listed.

### 7.10.2. Clinical Laboratory Evaluation Analyses

Descriptive statistics will be provided for the clinical laboratory results by scheduled time of evaluation and by treatment group and study part for the Safety Analysis Set, as well as for the change from baseline. The baseline value is defined as the last non-missing value before the initial administration of study treatment. In addition, mean change from baseline will be summarized for the maximum and minimum post-treatment values and the values at the End of Treatment visit.

Abnormal clinical laboratory results will be graded according to NCI CTCAE version 4.0, if applicable, and the grade will be presented in a by-subject data listing. A shift table, presenting by treatment group the 2-way frequency tabulation for baseline and the worst post-treatment value according to the NCI CTCAE grade, will be provided for clinical laboratory tests. Abnormal clinical laboratory test results deemed of clinical significance or of Grade 3 or 4 will be listed.

### 7.10.3. Vital Sign Analyses

Descriptive statistics will be provided for the vital signs measurements by scheduled time of evaluation and by treatment group and study part for the Safety Analysis Set, as well as for the change from baseline. The baseline value is defined as the last non-missing value before the initial administration of study treatment. In addition, mean change from baseline will be presented by treatment group for the maximum and minimum post-treatment values and the values at the End of Treatment visit.

### 7.10.4. Electrocardiogram Analyses

Descriptive statistics will be provided for the ECG measurements by scheduled time of evaluation and by treatment group for the Safety Analysis Set, as well as for the change from baseline. The baseline value is defined as the last non-missing value before the initial administration of study treatment. In addition, the number and percentage of subjects with ECG interval values meeting the criteria will be tabulated (eg, QTc ≤ 450 ms, > 450 to ≤ 480 ms, > 480 ms to ≤ 500 ms, and > 500 ms) and $QT_cF$ maximum changes from baseline (> 30 and > 60 ms) over all post-treatment evaluations will be summarized. ECG data will also be presented in the data listings.

### 7.10.5. Echocardiogram Analyses

Ejection fraction data will be summarized descriptively, for the Safety Analysis Set, including values at baseline and each time point along with mean change from baseline.

### 7.10.6. Analysis of Physical Examination Findings

Physical examination data will be listed.

#### 7.10.7. Concomitant Medication Analyses

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

## 7.11. Data Monitoring Committee

An independent DMC will be responsible for safeguarding the interests of study subjects, assessing the safety of the interventions during the trial, and monitoring the overall conduct of the trial. The DMC will also make recommendations about continuing, modifying, or stopping the trial. To enhance the integrity of the study, the DMC may also formulate recommendations relating to subject selection, recruitment, and management, improving adherence to protocol-specified regimens and subject retention, and data management and quality control procedures.

A separate DMC Charter will define the DMC membership, its roles and responsibilities, and the process for providing feedback to the Sponsor.

## 7.12. Sample Size Determination

For the purpose of sample size evaluation, the assumed rates of responders (subjects achieving a CR or PR) for the primary endpoint are 10% (placebo) and 35% (pexidartinib), respectively. Based on the use of a 2-sided, two-sample comparison of proportions at the alpha=0.05 level of significance by Fisher's exact test, a sample size of 126 ITT randomized subjects (63 per arm) provides 90% power to detect this magnitude of difference. The sample size was calculated using nQuery Advisor 7.0 with the module of two-group Fisher's exact test of equal proportions.

# 8. ETHICAL CONSIDERATIONS

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

# 9. SAFETY ASSESSMENT

## 9.1. Reporting Adverse Events and Serious Adverse Events

All AEs occurring after the subject signs the informed consent form and through the Post-Treatment Visit (28 ± 7 days after the last dose of study treatment), whether observed by the Investigator or reported by the subject, will be recorded on the AE eCRF page. Medical conditions (including laboratory values/vital signs that are out of range) that were diagnosed or known to exist prior to informed consent will be recorded as part of medical history. All SAEs are to be reported according to the procedures in Section 9.3 (SAE Reporting-Procedure for Investigators).

Always report diagnosis as the AE or SAE term(s). When a diagnosis is unavailable, report the primary sign or symptom as the AE or SAE term with additional details included in the narrative until the diagnosis becomes available.

If the signs and symptoms are distinct and do not suggest a common diagnosis, report them as individual entries of AE or SAE. For events that are serious due to hospitalization, the reason for hospitalization must be reported as the SAE (diagnosis or symptom requiring hospitalization). A procedure is not an AE or SAE, but the reason for the procedure may be an AE or SAE. Pre-planned (prior to signing the informed consent form) procedure or treatment requiring hospitalization for pre-existing conditions that do not worsen in severity should not be reported as SAEs (see Section 9.2 for definitions). For deaths, the underlying or immediate cause of death should always be reported as an SAE. Disease progression is a study endpoint and, consequently, should not be reported as an AE/SAE. However, when a subject dies from disease progression with no other immediate causes, “disease progression” should be reported as an SAE. In addition, any serious untoward event that may occur subsequent to the reporting period that the Investigator assesses as related to study treatment should also be reported and managed as an SAE.

At each visit, the Investigator will determine whether any AEs have occurred by evaluating the subject. Adverse events may be directly observed, reported spontaneously by the subject or by questioning the subject at each study visit. Subjects should be questioned in a general way, without asking about the occurrence of any specific symptoms. The Investigator must assess all AEs to determine seriousness, severity, and causality, in accordance with the definitions in Section 9.2. The Investigator’s assessment must be clearly documented in the site’s source documentation with the Investigator’s signature. All laboratory values must be appraised by the Investigator as to clinical significance. All abnormal laboratory values considered clinically significant by the Investigator must be recorded as an adverse event on the eCRF, and if serious, report as an SAE following the procedures in Section 9.3.

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

## 9.2. Definitions

### 9.2.1. Adverse Event

An AE is any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.[36]

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

### 9.2.2. Serious Adverse Event

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

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

Note: The term "life-threatening" in the definition of "serious" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.[36]

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

Note:

- A procedure is not an AE or SAE, but the reason for the procedure may be an AE or SAE.
- Pre-planned (prior to signing the informed consent form) procedures or treatment requiring hospitalizations for pre-existing conditions which do not worsen in severity are not SAEs.

### 9.2.3. Adverse Event Severity

All AEs will be graded (1 to 5; see below) according to the latest NCI CTCAE:

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

Severity vs. Seriousness

Severity is used to describe the intensity of a specific event while the event itself, however, may be of relatively minor medical significance (such as severe headache). This is not the same as "seriousness," which is based on subject/event outcome at the time of the event. For example, the NCI CTCAE Grade 4 (life-threatening consequences; urgent intervention indicated) is assessed based on unique clinical descriptions of severity for each AE, and these criteria may be different from those used for the assessment of AE seriousness. An AE assessed as Grade 4 based on the NCI CTCAE grades may or may not be assessed as serious based on the seriousness criteria.

### 9.2.4. Causality Assessment

The Investigator should assess causal relationship between an adverse event and the study treatment on the basis or his/her clinical judgment and the following definitions. The causality assessment should be made based on the available information and can be updated as new information becomes available.

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

### 9.2.5. Action Taken Regarding the Study Treatment

- 1 = Dose Not Changed: No change in study treatment dosage was made.
- 2 = Drug Withdrawn: The study product was permanently stopped.
- 3 = Dose Reduced: The dosage of study product was reduced.
- 4 = Drug Interrupted: The study product was temporarily stopped.

- 5 = Dose Increased: The dosage of study product was increased.

#### 9.2.6. Adverse Event Outcome

- 1 = Recovered/Resolved
  - The subject fully recovered from the adverse event with no residual effect observed.
- 2 = Recovered/Resolved with Sequelae
  - The residual effects of the adverse event are still present and observable.
  - Include sequelae/residual effects.
- 3 = Not Recovered/Not Resolved
  - The adverse event itself is still present and observable.
- 4 = Fatal

#### 9.2.7. Other Action Taken for Event

- 1 = None.
  - No treatment was required.
- 2 = Medication required.
  - Prescription and/or OTC medication was required to treat the adverse event.
- 3 = Hospitalization or prolongation of hospitalization required.
  - Hospitalization was required or prolonged because of the adverse event, whether or not medication was required.
- 4 = Other.

## 9.3. Serious Adverse Event Reporting Procedure for Investigators

### 9.3.1. Reporting by Investigators

All AEs and SAEs will be reported in the eCRF.

The following types of events should also be reported on the Daiichi Sankyo Serious Adverse Event Report (SAVER) Form within 24 hours of awareness:

- SAEs (Section 9.2.2)
- Hepatic events meeting combination abnormalities [ALT or AST ≥ 3 × ULN with simultaneous total bilirubin ≥ 2 × ULN] (potential Hy's Law case), both serious and non-serious

All AEs (serious and non-serious) must be reported with Investigator's assessment of the event's seriousness, severity, and causality to the blinded study treatment. A detailed

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

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

Please call the local SAE Hotline or your study monitor for any questions on SAE reporting (see Section 10.1.2.2).

### 9.3.2. Notifying Regulatory Authorities, Investigators, and Institutional Review Boards/Institutional Ethics Committees

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

In the US, upon receipt of the Sponsor's notification of SUSARs that occurred with the investigational product, unless delegated to the Sponsor, it is the Investigator's responsibility to inform the IRB per the Sponsor's instruction.

In the European Economic Area member states, it is the Sponsor's responsibility to report SUSARs to all IECs.

## 9.4. Procedures for Reporting Drug Exposure During Pregnancy and Birth Events

The Sponsor must be notified of any female subject or any male subject whose female partner who becomes pregnant while receiving or within 90 days of discontinuing the study treatment. Reporting after follow-up visit or early termination is done voluntarily by the Investigator.

Although pregnancy is not technically an AE, all pregnancies must be followed to conclusion to determine their outcome. This information is important for both drug safety and public health concerns. It is the responsibility of the Investigator or designee to report any pregnancy in a female subject or a male subject's female partner using the Exposure In Utero (EIU) Reporting Form. Please contact your study monitor to receive the EIU Reporting Form upon learning of a pregnancy. The Investigator should make every effort to follow the subject until completion of the pregnancy. If the outcome of the pregnancy meets the criteria for immediate classification as an SAE (ie, post-partum complications, spontaneous abortion, stillbirth, neonatal death, or congenital anomaly, including that in an aborted fetus), the Investigator should follow the procedures for reporting SAEs as outlined in Section 9.3. For reports of pregnancy in the female partner of a male subject, the EIU Reporting Form (or SAE form if associated with an adverse outcome) should be

completed with the subject's randomization number, initials, and date of birth, and details regarding the female partner should be entered in the narrative section.

# 10. STUDY ADMINISTRATIVE INFORMATION

## 10.1. Study Contacts

### 10.1.1. Sponsor

Daiichi Sankyo, Inc.
399 Thornall Street
Edison, NJ 08837, USA

### 10.1.2. Medical Monitor

#### 10.1.2.1. Sponsor Medical Monitor

[redacted]
Senior Director, Global Oncology R&D
Tel. : [redacted]
Cell: [redacted]
E-mail: [redacted]

#### 10.1.2.2. Contract Research Organization Medical Monitor

[redacted]
Novella Clinical
All Regions Except Europe Medical Monitor
[redacted]

[redacted]
Novella Clinical
EU Medical Monitor
[redacted]

### 10.1.3. SAE Reporting Contact

The Investigator will ensure that the SAE reporting form is completed and e-mailed/eFaxed to the following address within 24 hours of learning of the occurrence of any SAE:

Novella Clinical Safety Management Group
E-mail: pvgsafety@novellaclinical.com
eFax: +1 866 761 1274 (international lines specified in the Study Reference Manual)
Hotline: +1 866 758 2798 (international lines specified in the Study Reference Manual)

# 11. ADMINISTRATIVE REQUIREMENTS

## 11.1. Good Clinical Practice

The study will be conducted in accordance with the ICH Guideline for GCP and the appropriate regulatory requirement(s). The Investigator will be thoroughly familiar with the appropriate use of the study treatment as described in the protocol and the IB.

## 11.2. Data Quality Assurance

The Investigator is required to prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the study for each study subject. Study data will be entered into an eCRF by site personnel using a secure, validated web-based electronic data capture (EDC) application. The Sponsor will have access to all data upon entry in the EDC application.

Study monitors will discuss instances of missing or uninterpretable data with the Investigator and/or designee for resolution. Any changes to study data will be made to the eCRF and documented via an electronic audit trail associated with the affected eCRF.

## 11.3. Electronic Case Report Form Completion

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

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

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

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

The Sponsor or a designee will retain the eCRF data and corresponding audit trails. A copy of the final archival eCRF in the form of a compact disk or other electronic media will be placed in the Investigator's study file.

## 11.4. Data Management

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

To ensure the quality of clinical data across all subjects and sites, a Clinical Data Management review will be performed on subject data according to specifications given to the Sponsor or Sponsor designee. Data will be vetted both electronically and manually

for eCRFs, and the data will be electronically vetted by programmed data rules within the application. Queries generated by rules and raised by reviewers will be generated within the EDC application. During this review, subject data will be checked for consistency, omissions, and any apparent discrepancies.

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

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

## 11.5. Study Monitoring

Monitoring and auditing procedures developed or approved by the Sponsor will be followed, in order to comply with GCP guidelines.

All information recorded on the eCRFs for this study must be consistent with the subject's source documentation. During the course of the study, the study monitor will make study site visits to review protocol compliance, verify eCRFs against source documentation, assess drug accountability, and ensure that the study is being conducted according to pertinent regulatory requirements. The review of medical records will be performed in a manner to ensure that subject confidentiality is maintained.

## 11.6. Subject Information and Informed Consent

After the study has been fully explained, written informed consent will be obtained from either the subject or his/her guardian or legal representative prior to study participation. The method of obtaining and documenting the informed consent and the contents of the consent must comply with ICH-GCP and all applicable regulatory requirement(s).

## 11.7. Subject Confidentiality

In order to maintain subject privacy, all eCRFs, study treatment accountability records, study reports and communications will identify the subject by initials where permitted and/or by the assigned subject number. The subject's confidentiality will be maintained and will not be made publicly available to the extent permitted by the applicable laws and regulations.

## 11.8. Investigator Compliance

The Investigator will conduct the trial in compliance with the protocol provided by the Sponsor, and given approval/favorable opinion by the IRB/IEC and the appropriate regulatory authority (ies). Modifications to the protocol are not be made without agreement of both the Investigator and the Sponsor. Changes to the protocol will require written IRB/IEC approval/favorable opinion prior to implementation, except when the modification is needed to eliminate an immediate hazard(s) to subjects. The Sponsor or a designee will submit all protocol modifications to the appropriate regulatory authority (ies) in accordance with the governing regulations.

When immediate deviation from the protocol is required to eliminate an immediate hazard(s) to subjects, the Investigator will contact the Sponsor or a designee if circumstances permit, to discuss the planned course of action. Any departures from the protocol must be documented.

## 11.9. On-site Audits

Regulatory authorities, the IEC/IRB, and/or the Sponsor or its designee(s) may request access to all source documents, eCRFs, and other study documentation for on-site audit or inspection. Direct access to these documents must be guaranteed by the Investigator, who must provide support at all times for these activities.

## 11.10. Investigator and Site Responsibility for Drug Accountability

Accountability for the study treatment at the trial site is the responsibility of the Investigator. Drug accountability records including the study treatment's delivery date to the site, inventory at the site, use by each subject, and amount returned to the Sponsor or a designee (or disposal of the study treatment, if approved by the Sponsor) will be maintained by the clinical site. The Sponsor or its designee will review drug accountability at the site on an ongoing basis.

All material containing study treatment will be treated and disposed of as hazardous waste in accordance with governing regulations.

Also see Section 5.9 for specific details.

## 11.11. Product Complaints

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

For product complaints, refer to the Study Pharmacy Manual for instructions and details.

## 11.12. Study Closure

Within 90 days of the end of the study the Sponsor will notify the competent authorities and the IRBs/IECs in all member states where the study is being carried out that the study has ended.

Within 1 year of the end of the study, a summary of the clinical trial results will be submitted to the competent authorities and IRBs/IECs in all member states involved in the study.

Study participation by individual sites or the entire study may be prematurely terminated, if in the opinion of the Investigator or the Sponsor, there is sufficient reasonable cause. Written notification documenting the reason for study termination will be provided to the Investigator or the Sponsor by the terminating party.

Circumstances that may warrant termination include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to subjects
- Failure to enter subjects at an acceptable rate
- Insufficient adherence to protocol requirements
- Insufficient, incomplete, and/or unevaluable data
- Plans to modify, suspend or discontinue the development of the study treatment

Should the study be closed prematurely, the site will no longer be able to access the EDC application, will not have a right to use the EDC application, and will cease using the password or access materials once their participation in the study has concluded. In the event that any access devices for the EDC application have been provided, these will be returned to the Sponsor or designee once the site's participation in the study has concluded.

Within 15 business days of premature closure, the Sponsor must notify the competent authorities and IRBs/IECs of any member state where the study is being conducted, providing the reasons for study closure.

## 11.13. Study Documentation and Storage

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

Source documents are original documents, data, and records from which the subject's eCRF data are obtained. These include but are not limited to hospital records, clinical and office charts, laboratory and pharmacy records, diaries, microfiches, X-rays, and correspondence. eCRF entries may be considered source data if the eCRF is the site of the original recording (ie, there is no other written or electronic record of data).

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

- Subject files containing completed copy of eCRFs, informed consents, and supporting copies of source documentation (if kept).
- Study files containing the protocol with all amendments, Investigator's Brochure, copies of relevant essential documents required prior to commencing a clinical study, and all correspondence to and from the IEC/IRB and the Sponsor.
- Records related to the investigational product(s) including acknowledgment of receipt at site, accountability records and final reconciliation and applicable correspondence.

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

## 11.14. Record Retention

All essential documentation will be retained by the Investigator until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have lapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period, however, if required by the applicable regulatory requirements or by an agreement with the Sponsor. It is the responsibility of the Sponsor to inform the Investigator/institution as to when these documents no longer need to be retained.

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

## 11.15. Record Keeping

Records of subjects, source documents, monitoring visit logs, data correction forms, eCRFs, inventory of study product, regulatory documents (eg, protocol and amendments, IRB/IEC correspondence and approvals, approved and signed informed consent forms, Investigator's Agreement, clinical supplies receipts, distribution and return records), and other sponsor correspondence pertaining to the study must be kept in appropriate study files at the site. Source documents include all recordings and observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical study. These records will be retained in a secure file for the period required by the institution or site policy. Prior to transfer or destruction of these records, the Sponsor must be notified in writing and be given the opportunity to further store such records.

# 12. FINANCING AND INSURANCE

## 12.1. Finances

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

## 12.2. Reimbursement, Indemnity, and Insurance

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

# 13. USE OF INFORMATION

All information regarding pexidartinib supplied by the Sponsor to the Investigator is privileged and confidential information. The Investigator agrees to use this information to accomplish the study and will not use it for other purposes without consent from the Sponsor. It is understood that there is an obligation to provide the Sponsor with complete data obtained during the study. The information obtained from the clinical study will be used toward the development of pexidartinib and may be disclosed to regulatory authority(ies), other Investigators, corporate partners, public databases (eg, ClinicalTrials.gov, EU Clinical Trial Register), or consultants as required.

Upon completion of the clinical study and evaluation of results by the Sponsor, the hospital or institution and/or Investigator may publish or disclose the clinical trial results pursuant to the terms contained in the applicable Clinical Trial Agreement.

It is anticipated that the results of this study will be presented at scientific meetings and/or published in a peer-reviewed scientific or medical journal. A Publications Group comprised of Sponsor employees and study Investigators will be formed to oversee the publication of the study results that will reflect the experience of all participating study centers. Subsequently, individual Investigators may publish results from the study in compliance with their agreements with the Sponsor.

A prepublication manuscript or abstract is to be provided to the Sponsor a minimum of 30 days prior to the intended submission date of the manuscript or abstract to a publisher. Within 30 days after receipt by the Sponsor of the notification, the Sponsor shall inform the sites whether it has objections to the publication for reasons including, but not limited to, those defined below:

- If patentable subject matter is disclosed, the publication shall be delayed for a period not to exceed 90 days from the Sponsor's receipt of the proposed publication to allow time for the filing of patent applications covering patentable subject matter.
- If confidential information is contained in any proposed publication or public disclosure, such confidential information will be removed at the Sponsor's request.

# 14. REFERENCES

[1] Fletcher CDM, Bridge JA, Hogendoorn P, Mertens F. WHO Classification of Tumours of Soft Tissue and Bone, Fourth Edition. Lyon: IARC Press, 2013.

[2] Myers BW, Masi AT. Pigmented villonodular synovitis and tenosynovitis: a clinical epidemiologic study of 166 cases and literature review. Medicine. 1980;(59):223–38.

[3] Monaghan H, Salter DM, Al-Nafussi A. Giant cell tumour of tendon sheath (localized nodular tenosynovitis): clinicopathological features of 71 cases. J Clin Pathol 2001;(54):404–7.

[4] Ushijima M, Hashimoto H, Tsuneyoshi M, Enjoji M. Giant cell tumor of the tendon sheath (nodular tenosynovitis). A study of 207 cases to compare the large joint group with the common digit group. Cancer. 1986;57(4):875–84.

[5] Ushijima M, Hashimoto H, Tsuneyoshi M, Enjoji M. Pigmented villonodular synovitis. A clinicopathologic study of 52 cases. Acta Pathol Jpn. 1986;36(3):317–26.

[6] Rao AS, Vigorita VJ. Pigmented villonodular synovitis (giant-cell tumor of the tendon sheath and synovial membrane): A review of eighty-one cases. J Bone Joint Surg Am. 1984;66:76–94.

[7] Blay J-Y, El Sayadi H, Thiesse P, and Garret J. Letter to the editor: Complete response to imatinib in relapsing pigmented villonodular synovitis/tenosynovial giant cell tumor (PVNS/TGCT). Ann Oncol. 2008;19:821–2.

[8] Cassier PA, Gelderblom H, Stacchiotti S, et al. Efficacy of imatinib mesylate for the treatment of locally advanced and/or metastatic tenosynovial giant cell tumor/pigmented villonodular synovitis. Cancer. 2012;118(6):1649–55.

[9] Gelderblom H, Pérol D, Chevreau C, et al. An open-label international multicentric phase II study of nilotinib in progressive pigmented villo-nodular synovitis (PVNS) not amenable to a conservative surgical treatment. J Clin Oncol. 2013;31(suppl 15S):10516. [2013 American Society of Clinical Oncology (ASCO) Annual Meeting, Abstract #10516.]

[10] Cassier PA, Italiano A, Gomez-Roca CA, et al. CSF1R inhibition with emactuzumab in locally advanced diffuse-type tenosynovial giant cell tumours of the soft tissue: a dose-escalation and dose-expansion phase 1 study. Lancet Oncol. 2015;16(8):949-56.

[11] PLX3397 Investigator's Brochure, v.7. Berkeley, CA: Plexxikon Inc. Dec 2015.

[12] Tap WD, Wainberg ZA, Anthony SP, et al Structure-Guided Blockade of CSF1R Kinase in Tenosynovial Giant-Cell Tumor. N Engl J Med 2015;373:428-437.

[13] Ostergaard M, Peterfy C, Conaghan P, et al. OMERACT Rheumatoid Arthritis Magnetic Resonance Imaging Studies. Core set of MRI acquisitions, joint pathology

definitions, and the OMERACT RA-MRI scoring system. J Rheumatol. 2003;30(6):1385–6.

[14] Peterfy C, Guermazi A, Zaim S, et al. Whole-Organ Magnetic Resonance Imaging Score (WORMS) of the knee in osteoarthritis. Osteoarthritis Cartilage. 2004;12(3):177–90.

[15] West RB, Rubin BP, Miller MA, et al. A landscape effect in tenosynovial giant-cell tumor from activation of CSF1 expression by a translocation in a minority of tumor cells. Proc Natl Acad Sci USA. 2006;103(3):690–5.

[16] Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). Eur J Cancer. 2009;45:228–47.

[17] van der Heijden L, Gibbons CL, Dijkstra PD, et al. The management of diffuse-type giant cell tumour (pigmented villonodular synovitis) and giant cell tumour of tendon sheath (nodular tenosynovitis). J Bone Joint Surg Br. 2012;94(7):882–8.

[18] van der Heijden L, Gibbons CL, Hassan AB, et al. A multidisciplinary approach to giant cell tumors of tendon sheath and synovium: A critical appraisal of literature and treatment proposal. J Surg Oncol. 2013;107(4):433–45.

[19] O'Sullivan B, Cummings B, Catton C, et al. Outcome following radiation treatment for high-risk pigmented villonodular synovitis. Int J Radiat Oncol Biol Phys. 1995;32:777–86.

[20] Gerhardt JJ, Cocchiarella L, Lea RD. The Practical Guide to Range of Motion Assessment. Chicago, IL. Amer Med Assoc Press; 2002.

[21] Flockhart, DA. Drug Interactions: Cytochrome P450 Drug Interaction Table. Indiana University School of Medicine [2009]. Available from: http://medicine.iupui.edu/clinpharm/ddis/main-table/. Accessed October 22, 2014.

[22] Basch, Ethan, Autio, Karen A, Smith, Matthew R, et al, Effects of Cabozantinib on Pain and Narcotic Use in Patients with Castration-resistant Prostate Cancer: Results from a Phase 2 Nonrandomized Expansion Cohort, Eur Urol (2014), http://dx.doi.org/10.1016/j.eururo.2014.02.013.

[23] The Management of Postoperative Pain Working Group. VHA/DoD clinical practice guidelines for the management of postoperative pain. version 1.2. Washington, DC: Veterans Health Administration, Department of Defense; 2002. p. 44–5.

[24] Milliken, G.A.; Johnson D.E. The Analysis of Messy Data. In Vol. I: Designed Experiments. Chapman & Hall: New York; 1992.

[25] Little R J A., Rubin D B. Statistical Analysis with Missing Data. 2nd ed. New York: Wiley; 2002.

[26] Mallinckrodt C H, Clark W S, David S R. Accounting for dropout bias using mixed-effects models. J of Biopharm Statist. 2001; 11: 9–21.

[27] Siddiqui, O., Hung, H. M., O'Neil, R. MMRM versus LOCF: A comprehensive comparison based on simulation study and 25 NDA data sets. J of Biopharm Statist. 2009;.19: 227–46.

[28] Siddiqui, O. MMRM versus MI in Dealing with Missing Data—A Comparison Based on 25 NDA Data Sets, J of Biopharm Statist. 2011; 21(3): 423-36.

[29] Wilson, EB: Probable Inference, the Law of Succession, and Statistical Inference. J of the Amer Statist Assoc. 1927;22: 209.

[30] Newcombe, RG: Interval Estimation for the Difference Between Independent Proportions: Comparison of Eleven Methods. Statis in Med. 1998;17: 873–90.

[31] Lancaster HO. Significance tests in discrete distributions. J Am Statist Assoc. 1961;294(56):223–34.

[32] Lydersen S, Fagerland MW, Laake P. Recommended tests for association in 2 x 2 tables. Statist Med. 2009;28:1159–75.

[33] Westfall PH, Krishen A. Optimally weighted, fixed sequence and gatekeeper multiple testing procedures. J Statist Plan Infer. 2001;99(1):25–40.

[34] Dworkin RH, Turk DC, Wyrwich KW, et al. Interpreting the Clinical Importance of Treatment Outcomes in Chronic Pain Clinical Trials: IMMPACT Recommendations. J Pain. 2008; 9(2): 105-21.

[35] Farrara JT, Young Jr. JP, LaMoreaux L, et al. Clinical importance of changes in chronic pain intensity measured on an 11-point numerical pain rating scale. Pain. 2001; 94(2): 149–58.

[36] International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. ICH Harmonised Tripartite Guidelines. Clinical Safety Data Management: Definitions and Standards for Expedited Reporting E2A. Current Step 4 Revision. 27 October 1994. Available from: http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E2A/Step4/E2A_Guideline.pdf. Accessed November 4, 2014.

# 15. APPENDICES

## 15.1. List of Common CYP3A4 Inhibitors and Inducers

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

Source: Flockhart, DA. Drug Interactions: Cytochrome P450 Drug Interaction Table. Indiana University School of Medicine [2009]. Available from: http://medicine.iupui.edu/clinpharm/ddis/main-table/. Accessed October 22, 2014.

## 15.2. Detailed Study Procedures by Visit — Part 1

### 15.2.1. Screening (Day –42 to Day –1)

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

The following procedures *must* be performed within the 42-day period before P1-C1D1, unless otherwise noted, and the results *must* be obtained and evaluated for eligibility *prior to* the P1-C1D1 visit:

To be performed *before* any other procedures:

- Informed consent.

To be performed *before* any invasive procedures carried out on the same day:

- Vital signs, including blood pressure, pulse rate, and oral temperature;
- 12-lead ECG.

Other procedures to be performed:

- Medical history (including PVNS/GCT-TS treatment history and smoking history);
- Demographics, including ethnicity and race;
- Concomitant medications;
- BPI Worst Pain NRS item
    - This assessment is performed at the Screening Visit only. The recall period will be the preceding week. The subject's response must be documented in the medical notes;
- Worst Stiffness NRS item
    - This assessment is performed at the Screening Visit only. The recall period will be the preceding week. The subject's response must be documented in the medical notes;
- PROMIS Physical Function Scale
- Height and weight;
- Physical examination;
- AE assessment;
- Clinical laboratory tests — serum chemistry, hematology, liver function, hepatitis panel, hormone testing (as applicable), serum pregnancy testing (as applicable).

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

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

- ECHO or MUGA scanning;
- MRI of the affected joint within 56 days of P1-C1D1;
- Third-party blinded range-of-motion assessment of the affected joint;
- Dispense subject diary for recording daily BPI Worst Pain NRS, Worst Stiffness NRS and analgesic use during the 2-week period prior to P1-C1D1;
- Surgical Assessment Questionnaire.

To be performed any time during or after the Screening visit:

- Obtain archival tumor tissue.

### 15.2.2. Part 1 – Cycle 1 (Randomization)

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

- Subject randomization (time frame between randomization and first dose of study treatment can be up to 3 days prior to P1-C1D1).

### 15.2.3. Part 1–Cycle 1, Day 1 (P1-C1D1; Week 1)

To be performed *before* any invasive procedures:

- Vital signs, including blood pressure, pulse rate, and oral temperature;
- 12-lead ECG;
- PRO instruments, in the following order:
  - BPI Worst Pain NRS Item;
  - Worst Stiffness NRS item;
  - PROMIS Physical Function Scale;
  - Patient Global Rating of Concept item for carrying out every day physical activities;
  - EQ-5D-5L

To be performed *before* the first morning dose of study treatment:

- Review of outpatient PRO instruments;
- AE assessment;
- Concomitant medications;
- Analgesic use assessment;
- Most disturbing symptom assessment;
- HCRU and productivity;
- Clinical laboratory tests (only need to be done if they were not done within 72h of Day 1) — serum chemistry, hematology, coagulation, hormone levels, liver function, urinalysis;
- Blood sampling for PK and PDy analysis;
- Dispense study treatment bottles.

Subject is dosed in clinic.

To be performed *after* dosing:

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

To be performed 2 hours ± 10 minutes *after* dosing:

- 12-lead ECG.

### 15.2.4. Part 1–Cycle 1, Day 8 (P1-C1D8; Week 2) ± 2 days

- Clinical laboratory tests — liver function;
- AE assessment;
- Concomitant medications.

### 15.2.5. Part 1–Cycle 1, Day 15 (P1-C1D15; Week 3) ± 2 days

To be performed *before* any invasive procedures:

- Vital signs, including blood pressure, pulse rate, and oral temperature;
- 12-lead ECG.

To be performed *before* the morning dose:

- AE assessment;
- Concomitant medications, including analgesics;
- Treatment compliance assessment;
- Clinical laboratory tests — liver function, hematology;
- Blood sampling for PK and PDy analysis;

Subject is dosed in clinic.

To be performed *after* the morning dose:

- Record the dose (subject diary, source records, eCRF);
- Re-dispense study treatment bottles;
- Blood sampling for PK analysis at various post-dose time points (see Section 6.4.16).

To be performed 2 hours ± 10 minutes *after* dosing:

- 12-lead ECG.

### 15.2.6. Part 1–Cycle 1, Day 22 (P1-C1D22; Week 4) ± 2 days

- Clinical laboratory tests — liver function;
- AE assessment;
- Concomitant medications.

### 15.2.7. Part 1–Cycle 2, Day 1 (P1-C2D1; Week 5) ± 2 days

To be performed before any invasive procedures:

- Vital signs, including blood pressure, pulse rate, and oral temperature;
- AE assessment;
- Concomitant medications, including analgesics;
- HCRU and productivity;
- Treatment compliance assessment.

Other procedures to be performed:

- Physical examination;
- Clinical laboratory tests — serum chemistry, hematology, liver function, serum pregnancy testing (as applicable);
- Blood sampling for PK and PDy analysis;
- Dispense study treatment bottles

### 15.2.8. Part 1–Cycle 2, Day 8 (P1-C2D8; Week 6) ± 2 days

To be performed before any invasive procedures:

- Clinical laboratory tests — liver function;
- AE assessment.
- Concomitant medications.

### 15.2.9. Part 1–Cycle 2, Day 15 (P1-C2D15; Week 7) ± 2 days

- Clinical laboratory tests — liver function;
- AE assessment;
- Concomitant medications.

### 15.2.10. Part 1–Cycle 2, Day 22 (P1-C2D22; Week 8) ± 2 days

To be performed before any invasive procedures:

- Clinical laboratory tests — liver function;
- AE assessment.
- Concomitant medications.

### 15.2.11. Part 1–Cycle 3, Day 1 (P1-C3D1; Week 9) ± 7 days

To be performed *before* any invasive procedures:

- Vital signs, including blood pressure, pulse rate, and oral temperature;
- PRO instruments, in the following order:

- BPI Worst Pain NRS item;
- Worst Stiffness NRS item;
- PROMIS Physical Function Scale
- Patient Global Rating of Concept item for carrying out every day physical activities;
- EQ-5D-5L.

Other procedures to be performed:

- Review outpatient PRO instruments;
- AE assessment;
- Concomitant medications, including analgesics;
- HCRU and productivity;
- Treatment compliance assessment;
- Clinical laboratory tests — serum chemistry, hematology, liver function, serum pregnancy testing (as applicable);
- Random post-dose blood sampling for PK and PDy analysis;
- Dispense study treatment bottles.
- Analgesic use assessment.

#### 15.2.12. Part 1–Cycle 3, Day 15 (P1-C3D15; Week 11) ± 7 days

To be performed before any invasive procedures:

- Clinical laboratory tests — liver function;
- AE assessment.
- Concomitant medications.

#### 15.2.13. Part 1–Cycle 4, Day 1 (P1-C4D1; Week 13) ± 7 days

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

- ECHO or MUGA scanning;
- MRI of the affected joint (with local assessment of progression status). The Investigator may request a centrally read blinded MRI to confirm progression, eg, if a subject's mid-study clinical profile or local radiological assessment indicates progression;
- Third-party blinded range-of-motion assessment of the affected joint.

To be performed *before* any invasive procedures:

- Vital signs, including blood pressure, pulse rate, and oral temperature.

Other procedures to be performed:

- Dispense study treatment bottles;
- AE assessment;
- Concomitant medications, including analgesics;
- HCRU and productivity;
- Treatment compliance assessment;
- Physical examination;
- Clinical laboratory tests — serum chemistry, hematology, liver function, serum pregnancy testing (as applicable), and urinalysis.

### 15.2.14. Part 1–Cycle 5, Day 1 (P1-C5D1; Week 17) ± 7 days

To be performed *before* any invasive procedures:

- Vital signs, including blood pressure, pulse rate, and oral temperature;
- PRO instruments, in the following order:
  - BPI Worst Pain NRS Item;
  - Worst Stiffness NRS item;
  - PROMIS Physical Function Scale;
  - Patient Global Rating of Concept item for carrying out every day physical activities;
  - EQ-5D-5L.

Other procedures to be performed:

- Dispense study treatment bottles;
- Analgesic use assessment;
- Review outpatient PRO instruments;
- AE assessment;
- Concomitant medications, including analgesics;
- HCRU and productivity;
- Treatment compliance assessment;
- Random post-dose blood sampling for PK and PDy analysis;
- Clinical laboratory tests — serum chemistry, hematology, liver function, serum pregnancy testing (as applicable).

### 15.2.15. Part 1–Cycle 6, Day 1 (P1-C5D1; Week 21) ± 7 days

To be performed *before* any invasive procedures:

- Vital signs, including blood pressure, pulse rate, and oral temperature;

Other procedures to be performed:

- Dispense study treatment bottles;
- AE assessment;
- Concomitant medications, including analgesics;
- HCRU and productivity;
- Treatment compliance assessment;
- Clinical laboratory tests — serum chemistry, hematology, liver function, serum pregnancy testing (as applicable).

### 15.2.16. Part 1 Completion visit/Early Termination Visit (Week 25) ± 7 days

For subjects continuing to Part 2, see Section 15.3.1 instead.

To be performed within the 7-day period *before* the visit:

- ECHO or MUGA scanning;
- MRI of the affected joint (with local assessment of progression status);
- Third-party blinded range-of-motion assessment of affected joint.

To be performed *before* any invasive procedures:

- Vital signs, including blood pressure, pulse rate, and oral temperature;
- 12-lead ECG.
- PRO instruments, in the following order:
    - BPI Worst Pain NRS Item;
    - Worst Stiffness NRS item;
    - PROMIS Physical Function Scale;
    - Patient Global Rating of Concept item for carrying out every day physical activities;
    - EQ-5D-5L;
    - Patient Global Impression of Change item for tumor-related stiffness.

Other procedures to be performed:

- Review outpatient PRO instruments;
- AE assessment;
- Concomitant medications, including analgesics;
- HCRU and productivity.
- Treatment compliance assessment;
- Analgesic use assessment;

- Weight;
- Physical examination;
- Clinical laboratory tests — serum chemistry, hematology, coagulation, liver function, hormone levels, serum pregnancy testing (as applicable), urinalysis;
- Surgical Assessment Questionnaire.
- For subjects who undergo surgical resection of the tumor within 12 weeks of the last dose of study treatment, refer to Section 15.4 for collection of surgery related data. If a subject has surgery within 4 weeks of the last dose, the subject does not need to have the 28 Day Post-Treatment Visit evaluations. However, if a subject has surgery after 4 weeks of the last dose, the subject should have the 28 Day Post-Treatment Visit evaluations. None of these subjects need to have the End-of-Study Visit.

As of 30 Sep 2016, subjects who wish to continue onto the open label part of this study (Part 2) will be unblinded after completion of the end of Part 1 assessments (Part 1 Completion visit/Early Termination visit) and those on placebo will be discontinued; subjects on pexidartinib in Part 1 may continue into Part 2 to continue to receive pexidartinib. Subjects who discontinue Part 1 early, should complete the end of Part 1 assessments (Part 1 Completion visit/Early Termination) at or before the time of their last treatment (MRI or range of motion assessments do not need to be repeated, if completed in the previous 28 days).

### 15.2.17. Part 1 28 Day Post-Treatment Visit (last dose + 28 days) ± 7 days

As of 30 Sep 2016, subjects who wish to continue onto the open label part of this study (Part 2) will be unblinded after completion of the end of Part 1 assessments (Part 1 Completion visit/Early Termination visit) and those on placebo will be discontinued and will not need to complete the Part 1 28 Day Post-Treatment Visit and associated procedures.

This visit is scheduled 28 ± 7 days after the last dose of study treatment.

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

- MRI of the affected joint (for subjects who withdraw from the study for reasons other than progression; local assessment of progression status will be recorded);
- Third-party blinded range-of-motion assessment of the affected joint.

To be performed *before* any invasive procedures:

- Vital signs, including blood pressure, pulse rate, and oral temperature;
- 12-lead ECG;
- PRO instruments, in the following order:
  - BPI Worst Pain NRS item;
  - Worst Stiffness NRS item;

- PROMIS Physical Function Scale;
- Patient Global Rating of Concept item for carrying out every day physical activities;
- EQ-5D-5L;
- Patient Global Impression of Change item for tumor-related stiffness.

Other procedures to be performed:

- Review outpatient PRO instruments;
- AE assessment;
- Concomitant medications, including analgesics;
- HCRU and productivity;
- Analgesic use assessment;
- Weight;
- Physical examination;
- ECHO or MUGA scanning (only if > 3 months have elapsed since the previous scan);
- Clinical laboratory tests — serum chemistry, hematology, coagulation, liver function, hormone levels, serum pregnancy testing (if applicable), urinalysis;
- Surgical Assessment Questionnaire.
- For subjects terminating the study because of progression, document if they plan to undergo any new PVNS/GCT-TS therapy, including surgery, during the 28-day period (± 7 days) after their last dose of study treatment.
- For subjects who undergo surgical resection of the tumor within 12 weeks of the last dose of study treatment, refer to Section 15.4 for collection of surgery related data.

#### 15.2.18. Part 1 End-of-Study/12 Week Post-Treatment Visit (12 weeks ± 7 days after the last dose)

As of 30 Sep 2016, subjects who wish to continue onto the open label part of this study (Part 2) will be unblinded after completion of the end of Part 1 assessments (Part 1 Completion visit/Early Termination visit) and those on placebo will be discontinued and will not need to complete the Part 1 End-of-study/12 Week Post-Treatment Visit and associated procedures.

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

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

- MRI of the affected joint (with local assessment of progression status)

Other procedures to be performed:

- Clinical laboratory tests — serum pregnancy testing (if applicable);
- AE assessment;
- Concomitant medications;
- Ask the subject if s/he plans to begin any new PVNS/GCT-TS therapy, including surgery. For subjects who undergo surgical resection of the tumor within 12 weeks of the last dose of study treatment, refer to Section 15.4 for collection of surgery related data.
- For other subjects, terminate the subject from the study.

## 15.3. Detailed Study Procedures by Visit — Part 2

If the subject is known to have been on pexidartinib treatment in Part 1, then visits and associated procedures are only required on Day 1 of each cycle in Part 2.

### 15.3.1. Part 2–Cycle 1, Day 1 (P2-C1D1; Week 25)

For subjects continuing to Part 2, the P2-C1D1 visit will serve as both the Part 1 Completion visit and the first visit of Part 2. Some procedures for both visits can occur on the same day.

The following procedures are performed as part of the P1-Completion visit.

To be performed within the 7-day period *before* the P2-C1D1 visit:

- ECHO or MUGA scanning;
- MRI of the affected joint (with local assessment of progression status). The Investigator may request a centrally read MRI to confirm progression, eg, if a subject's mid-study clinical profile or local radiological assessment indicates progression.
- Third-party blinded range-of-motion assessment of the affected joint.

To be performed *before* any invasive procedures:

- Vital signs, including blood pressure, pulse rate, and oral temperature;
- PRO instruments, in the following order:
    - BPI Worst Pain NRS item;
    - Worst Stiffness NRS item;
    - PROMIS Physical Function Scale;
    - EQ-5D-5L.

To be performed *before* dosing at the P2-C1D1 visit:

- Review outpatient PRO instruments;
- AE assessment;
- Concomitant medications, including analgesics;
- Treatment compliance assessment;
- Analgesic use assessment.
- Weight;
- Physical examination;
- Clinical laboratory tests - serum chemistry, hematology, coagulation, liver function, hormone levels, serum pregnancy testing (as applicable), urinalysis.

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

The following procedures will be performed as part of the P2-C1D1visit.

To be performed *before* dosing:

- Blood sampling for PK and PDy analysis

Subject is dosed in clinic.

To be performed *after* dosing:

- Record the dose (subject diary, source records, eCRF);
- Dispense study treatment bottles.

To be performed 2 hours ± 10 minutes *after* dosing:

- 12-lead ECG.

### 15.3.2. Part 2–Cycle 1, Day 8 (P2-C1D8; Week 26) ± 2 days

- Clinical laboratory tests — liver function;
- AE assessment;
- Concomitant medications.

### 15.3.3. Part 2–Cycle 1, Day 15 (P2-C1D15; Week 27) ± 2 days

To be performed *before* any invasive procedures:

- Vital signs, including blood pressure, pulse rate, and oral temperature;
- 12-lead ECG.

To be performed *before* the morning dose:

- Blood sampling for PK and PDy analysis;
- Clinical laboratory tests — hematology, liver function;

Subject is dosed in clinic.

To be performed *after* the morning dose:

- Record the dosing (subject diary, source records, eCRF);
- Blood sampling for PK analysis at various post-dose time points (see Section 6.4.16 for details).

To be performed 2 hours ± 10 minutes *after* dosing:

- 12-lead ECG.

Other procedures to be performed:

- AE assessment;
- Concomitant medications, including analgesics;
- Treatment compliance assessment;

#### 15.3.4. Part 2–Cycle 1, Day 22 (P2-C1D22; Week 28) ± 2 days

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

#### 15.3.5. Part 2–Cycle 2, Day 1 (P2-C2D1; Week 29) ± 2 days

To be performed *before* any invasive procedures:

- Vital signs, including blood pressure, pulse rate, and oral temperature.

Other procedures to be performed:

- Dispense study treatment bottles;
- AE assessment;
- Concomitant medications, including analgesics;
- Treatment compliance assessment;
- Random post-dose blood sampling for PK and PDy analysis;
- Clinical laboratory tests - serum chemistry, hematology, liver function; serum pregnancy testing (if applicable);
- Physical examination.

#### 15.3.6. Part 2–Cycle 2, Day 8 (P2-C2D8; Week 30) ± 2 days

- Clinical laboratory tests — liver function;
- AE assessment.
- Concomitant medications.

#### 15.3.7. Part 2–Cycle 2, Day 15 (P2-C2D15; Week 31) ± 2 days

- Clinical laboratory tests — liver function;
- AE assessment;
- Concomitant medications.

#### 15.3.8. Part 2–Cycle 2, Day 22 (P2-C2D22; Week 32) ± 2 days

To be performed before any invasive procedures:

- Clinical laboratory tests — liver function;
- AE assessment.
- Concomitant medications.

#### 15.3.9. Part 2–Cycle 3, Day 1 (P2-C3D1; Week 33) ± 7 days

To be performed *before* any invasive procedures:

- Vital signs, including blood pressure, pulse rate, and oral temperature.

Other procedures to be performed:

- AE assessment;
- Concomitant medications, including analgesics;
- Treatment compliance assessment;
- Clinical laboratory tests — serum chemistry, hematology, liver function; serum pregnancy testing (if applicable);
- Dispense study treatment bottles.

#### 15.3.10. Part 2–Cycle 3, Day 15 (P2-C3D15; Week 35) ± 7 days

To be performed before any invasive procedures:

- Clinical laboratory tests — liver function;
- AE assessment.
- Concomitant medications.

#### 15.3.11. Part 2–Cycle 4, Day 1 (P2-C4D1; Week 37) ± 7 days

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

- ECHO or MUGA scanning;
- MRI of the affected joint (with local assessment of progression status);
- Third-party blinded range-of-motion assessment of the affected joint;

To be performed *before* any invasive procedures:

- Vital signs, including blood pressure, pulse rate, and oral temperature;
- PRO instruments, in the following order:
  - BPI Worst Pain NRS Item
  - Worst Stiffness NRS item
  - PROMIS Physical Function Scale
  - EQ-5D-5L

Other procedures to be performed:

- Dispense study treatment bottles.
- Review outpatient PRO instruments;
- AE assessment;
- Concomitant medications, including analgesics;
- Treatment compliance assessment;
- Physical examination;
- Clinical laboratory tests — serum chemistry, hematology, liver function, serum pregnancy testing (if applicable), urinalysis;
- Analgesic use assessment.

### 15.3.12. Part 2–Cycle 5, Day 1 (P2-C5D1; Week 41) ± 7 days

To be performed before any invasive procedures:

- Vital signs, including blood pressure, pulse rate, and oral temperature.

Other procedures to be performed:

- Dispense study treatment bottles;
- AE assessment;
- Concomitant medications, including analgesics;
- Treatment compliance assessment;
- Clinical laboratory tests — serum chemistry, hematology, liver function, serum pregnancy testing (if applicable).

### 15.3.13. Part 2–Cycle 6, Day 1 (P2-C6D1; Week 45) ± 7 days

To be performed *before* any invasive procedures:

- Vital signs, including blood pressure, pulse rate, and oral temperature.

Other procedures to be performed:

- Dispense study treatment bottles;
- AE assessment;
- Concomitant medications, including analgesics;
- Treatment compliance assessment;
- Clinical laboratory tests — serum chemistry, hematology, liver function, serum pregnancy testing (if applicable);

### 15.3.14. Part 2–Cycle 7, Day 1 (P2-C7D1; Week 49) ± 7 days

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

- ECHO or MUGA scanning;
- MRI of the affected joint (with local assessment of progression status);
- Third-party blinded range-of-motion assessment of the affected joint.

To be performed *before* any invasive procedures:

- Vital signs, including blood pressure, pulse rate, and oral temperature;
- 12-lead ECG (performed every 24 weeks from this point forward, ie, P2-C13D1, P2-C19D1, etc.);
- PRO instruments, in the following order:
    - BPI Worst Pain NRS Item
    - Worst Stiffness NRS item
    - PROMIS Physical Function Scale
    - EQ-5D-5L

To be performed *before* dosing:

- Blood sampling for hormone levels (performed every 24 weeks from this point forward, ie, P2-C13D1, P2-C19D1, etc.);
- Dispense study treatment bottles.

Subject is dosed in clinic.

To be performed *after* the morning dose:

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

Other procedures to be performed:

- Review outpatient PRO instruments;
- AE assessment;
- Concomitant medications, including analgesics;
- Treatment compliance assessment;
- Physical examination;
- Clinical laboratory tests — serum chemistry, hematology, liver function, serum pregnancy testing (if applicable);
- Analgesic use assessment;
- Surgical Assessment Questionnaire.
- For subjects who undergo surgical resection of the tumor within 12 weeks of the last dose of study treatment, refer to Section 15.4 for collection of surgery related data. If a subject has surgery within 4 weeks of the last dose, the subject does not need to have the Post-Treatment Visit evaluations. However, if a subject has surgery after 4 weeks of the last dose, the subject should have the Post-Treatment Visit evaluations. None of these subjects need to have the End-of-Study Visit.

#### 15.3.15. Part 2–Cycle 10+, Day 1 (P2-C10+D1; Week 61+) ± 7 days

The procedures described below are performed at P2-C10D1 ± 7 days and every 12 weeks thereafter (eg, P2-C13, P2-C16).

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

- MRI of the affected joint (with local assessment of progression status);
- Third-party blinded range-of-motion assessment of the affected joint.

To be performed *before* any invasive procedures:

- Vital signs, including blood pressure, pulse rate, and oral temperature;
- PRO instruments, in the following order:
  - BPI Worst Pain NRS Item
  - Worst Stiffness NRS item
  - PROMIS Physical Function Scale
  - EQ-5D-5L

Other procedures to be performed:

- Dispense study treatment bottles.
- Review outpatient PRO instruments;
- AE assessment;
- Concomitant medications, including analgesics;

- Treatment compliance assessment;
- Physical examination;
- Clinical laboratory tests — serum chemistry, hematology, liver function, serum pregnancy testing (if applicable);
- Analgesic use assessment;

### 15.3.16. Post-Treatment Visit (Part 2)

The Post-treatment Visit is scheduled 28 ± 7 days after the last dose of study treatment.

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

- MRI of the affected joint (with local assessment of progression status);
- Third-party blinded range-of-motion assessment of the affected joint.

To be performed *before* any invasive procedures:

- Vital signs, including blood pressure, pulse rate, and oral temperature;
- 12-lead ECG;
- PRO instruments (if not done within the last 30 days), in the following order:
    - BPI Worst Pain NRS Item
    - Worst Stiffness NRS item
    - PROMIS Physical Function Scale
    - EQ-5D-5L

Other procedures to be performed:

- Review outpatient PRO instruments;
- AE assessment;
- Concomitant medications, including analgesics;
- Treatment compliance assessment;
- Analgesic use assessment;
- Weight;
- Physical examination;
- ECHO or MUGA scanning (only if >3 months have elapsed since the previous scan);
- Clinical laboratory tests — serum chemistry, hematology, coagulation, liver function, hormone levels, serum pregnancy testing (as applicable), urinalysis;
- Surgical Assessment Questionnaire;
- For subjects terminating the study because of progression, document if they plan to undergo any new PVNS/GCT-TS therapy, including surgery, during the 28-day period (± 7 days) after their last dose of study treatment.
- For subjects who undergo surgical resection of the tumor within 12 weeks of the last dose of study treatment, refer to Section 15.4 for collection of surgery related data.

### 15.3.17. End-of-Study or Early Termination Visit

The End-of-Study/Early Termination Visit is scheduled 12 weeks ± 7 days after the last dose of study treatment or before any new PVNS/GCT-TS therapy, including surgery, whichever occurs first.

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

- MRI of the affected joint (with local assessment of progression status);

Other procedures to be performed:

- Clinical laboratory tests - serum pregnancy testing (if applicable);
- AE assessment;
- Concomitant medications;
- Ask the subject if s/he has begun any new PVNS/GCT-TS therapy, including surgery; For subjects who undergo surgical resection of the tumor within 12 weeks of the last dose of study treatment, refer to Section 15.4 for collection of surgery related data.
- For other subjects, terminate the subject from the study.

## 15.4. Detailed Study Procedures by Visit — Surgical Outcome

For subjects who undergo surgical resection of the tumor within 12 weeks of the last dose of study treatment, they will remain on the study and follow a different study visit schedule to obtain data on the surgical procedure and its outcome. There is no need to have the End-of-Study visit.

If a subject has surgery within 4 weeks of the last dose of study treatment, the subject does not need to have the Post-Treatment Visit evaluations per Section 15.2 and Section 15.3, but will need to have the safety lab tests (blood chemistry, hematology, liver function tests, coagulation tests, urinalysis, and serum pregnancy test) and an ECG performed at least 7 days after the last dose of study treatment, but prior to surgery.

If a subject has surgery after 4 weeks of the last dose of study treatment, the subject should have the Post-Treatment Visit evaluations per Section 15.2 and Section 15.3.

### 15.4.1. Four weeks Prior to Surgery

For subjects undergoing surgical resection, the following procedures are performed within the 4-week period *before* surgery:

- MRI of the affected joint (Only perform if not done within 12 weeks prior to the surgery)
- Third-party blinded range-of-motion assessment of the affected joint.
- PRO instruments, in the following order:
    - BPI Worst Pain NRS item;
    - Worst Stiffness NRS item;
    - PROMIS Physical Function Scale;
- Collection of SAEs (Note: hospitalization for the surgery is not considered as SAE)
- Reasons for surgery

### 15.4.2. During or shortly after Surgery

- Surgical procedures and findings
- Tumor sample submission
- Collection of SAEs

### 15.4.3. 4 Months (± 2 weeks) after Surgery

- MRI of the affected joint
- Third-party blinded range-of-motion assessment of the affected joint.
- PRO instruments, in the following order:
    - BPI Worst Pain NRS item;

- Worst Stiffness NRS item;

- Collection of SAEs (Note: hospitalization for the surgery is not considered as SAE)
- Disease Recurrence

### 15.4.4. 8, 12, 18, and 24 Months (± 2 weeks) after Surgery

- Disease Recurrence
- No End-of-Study visit is required, however an End of Study eCRF will be completed at this time

## 15.5. Brief Pain Inventory (BPI) Worst Pain Numeric Rating Scale (NRS) Item

The following question asks about pain at the site of your tumor.

Please rate your pain by circling the one number that best describes your pain at its worst in the last 24 hours.

| 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
|---|---|---|---|---|---|---|---|---|---|---|
| No pain | | | | | | | | | | Pain as bad as you can imagine |

## 15.6. Worst Stiffness NRS item

The following question asks about stiffness at the site of your tumor.

Please rate your stiffness by circling the one number that best describes your stiffness at its worst in the last 24 hours.

| 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
|---|---|---|---|---|---|---|---|---|---|---|
| No stiffness | | | | | | | | | | Stiffness as bad as you can imagine |

## 15.7. PROMIS Physical Function Scale

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

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

| | | Without any difficulty | With a little difficulty | With some difficulty | With much difficulty | Unable to do |
|---|---|---|---|---|---|---|
| PFA23 | Are you able to go for a walk of at least 15 minutes? ..... | ☐ 5 | ☐ 4 | ☐ 3 | ☐ 2 | ☐ 1 |
| PFA16r1 | Are you able to dress yourself, including tying shoelaces and buttoning up your clothes? ..... | ☐ 5 | ☐ 4 | ☐ 3 | ☐ 2 | ☐ 1 |
| | | **Not at all** | **Very little** | **Somewhat** | **Quite a lot** | **Cannot do** |
| PFB54 | Does your health now limit you in going OUTSIDE the home, for example to shop or visit a doctor's office? ..... | ☐ 5 | ☐ 4 | ☐ 3 | ☐ 2 | ☐ 1 |
| PFA4 | Does your health now limit you in doing heavy work around the house like scrubbing floors, or lifting or moving heavy furniture? ..... | ☐ 5 | ☐ 4 | ☐ 3 | ☐ 2 | ☐ 1 |
| | | **Without any difficulty** | **With a little difficulty** | **With some difficulty** | **With much difficulty** | **Unable to do** |
| PFA12 | Are you able to push open a heavy door? ..... | ☐ 5 | ☐ 4 | ☐ 3 | ☐ 2 | ☐ 1 |
| PFA14r1 | Are you able to carry a heavy object (over 10 pounds/5 kg)? ..... | ☐ 5 | ☐ 4 | ☐ 3 | ☐ 2 | ☐ 1 |
| | | **Not at all** | **Very little** | **Somewhat** | **Quite a lot** | **Cannot do** |
| PFB1 | Does your health now limit you in doing moderate work around the house like vacuuming, sweeping floors or carrying in groceries? ..... | ☐ 5 | ☐ 4 | ☐ 3 | ☐ 2 | ☐ 1 |
| PFA5 | Does your health now limit you in lifting or carrying groceries? ..... | ☐ 5 | ☐ 4 | ☐ 3 | ☐ 2 | ☐ 1 |
| | | **Without any difficulty** | **With a little difficulty** | **With some difficulty** | **With much difficulty** | **Unable to do** |
| PFA21 | Are you able to go up and down stairs at a normal pace?..... | ☐ 5 | ☐ 4 | ☐ 3 | ☐ 2 | ☐ 1 |
| PFA42 | Are you able to carry a laundry basket up a flight of stairs? ..... | ☐ 5 | ☐ 4 | ☐ 3 | ☐ 2 | ☐ 1 |
| PFA10 | Are you able to stand for one hour? ..... | ☐ 5 | ☐ 4 | ☐ 3 | ☐ 2 | ☐ 1 |

| | | Without any difficulty | With a little difficulty | With some difficulty | With much difficulty | Unable to do |
|---|---|---|---|---|---|---|
| | | **Not at all** | **Very little** | **Somewhat** | **Quite a lot** | **Cannot do** |
| PFA3 | Does your health now limit you in bending, kneeling, or stooping? ..... | ☐ 5 | ☐ 4 | ☐ 3 | ☐ 2 | ☐ 1 |
| | | **Without any difficulty** | **With a little difficulty** | **With some difficulty** | **With much difficulty** | **Unable to do** |
| PFA13 | Are you able to exercise for an hour? ..... | ☐ 5 | ☐ 4 | ☐ 3 | ☐ 2 | ☐ 1 |

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

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

| | | Without any difficulty | With a little difficulty | With some difficulty | With much difficulty | Unable to do |
|---|---|---|---|---|---|---|
| PFB34 | Are you able to change a light bulb overhead?..... | ☐ 5 | ☐ 4 | ☐ 3 | ☐ 2 | ☐ 1 |
| PFA16r1 | Are you able to dress yourself, including tying shoelaces and buttoning up your clothes? ..... | ☐ 5 | ☐ 4 | ☐ 3 | ☐ 2 | ☐ 1 |
| | | **Not at all** | **Very little** | **Somewhat** | **Quite a lot** | **Cannot do** |
| PFB54 | Does your health now limit you in going OUTSIDE the home, for example to shop or visit a doctor's office? ..... | ☐ 5 | ☐ 4 | ☐ 3 | ☐ 2 | ☐ 1 |
| PFA4 | Does your health now limit you in doing heavy work around the house like scrubbing floors, or lifting or moving heavy furniture? ..... | ☐ 5 | ☐ 4 | ☐ 3 | ☐ 2 | ☐ 1 |
| | | **Without any difficulty** | **With a little difficulty** | **With some difficulty** | **With much difficulty** | **Unable to do** |
| PFA12 | Are you able to push open a heavy door? ..... | ☐ 5 | ☐ 4 | ☐ 3 | ☐ 2 | ☐ 1 |
| PFB28r1 | Are you able to lift 10 pounds (5 kg) above your shoulder?..... | ☐ 5 | ☐ 4 | ☐ 3 | ☐ 2 | ☐ 1 |
| PFA14r1 | Are you able to carry a heavy object (over 10 pounds/5 kg)? ..... | ☐ 5 | ☐ 4 | ☐ 3 | ☐ 2 | ☐ 1 |
| | | **Not at all** | **Very little** | **Somewhat** | **Quite a lot** | **Cannot do** |
| PFB1 | Does your health now limit you in doing moderate work around the house like vacuuming, sweeping floors or carrying in groceries? ..... | ☐ 5 | ☐ 4 | ☐ 3 | ☐ 2 | ☐ 1 |
| PFA5 | Does your health now limit you in lifting or carrying groceries? ..... | ☐ 5 | ☐ 4 | ☐ 3 | ☐ 2 | ☐ 1 |
| | | **Without any difficulty** | **With a little difficulty** | **With some difficulty** | **With much difficulty** | **Unable to do** |
| PFA42 | Are you able to carry a laundry basket up a flight of stairs? ..... | ☐ 5 | ☐ 4 | ☐ 3 | ☐ 2 | ☐ 1 |
| PFA13 | Are you able to exercise for an hour? .. | ☐ 5 | ☐ 4 | ☐ 3 | ☐ 2 | ☐ 1 |

## 15.8. EQ-5D-5L

**Health Questionnaire**

**English version for the USA**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Under each heading, please check the ONE box that best describes your health TODAY

**MOBILITY**

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

**SELF-CARE**

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

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

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

**PAIN / DISCOMFORT**

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

**ANXIETY / DEPRESSION**

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


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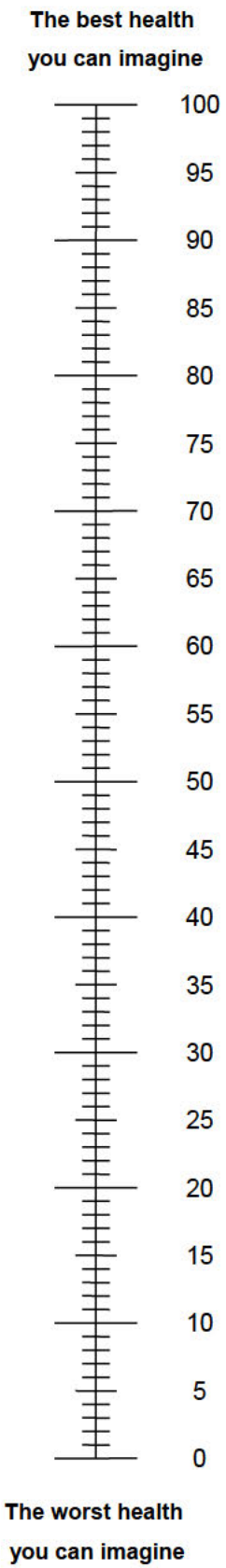
We would like to know how good or bad your health is TODAY.

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

YOUR HEALTH TODAY = ☐

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## 15.9. Patient Global Impression of Change and Rating of Concept Items

***Patient Global Rating of Concept – Physical Functioning***

***Please rate your tumor-related physical functioning. Please focus on your ability to carry out your everyday physical activities, such as walking, climbing stairs, or carrying groceries.***

*How much has your tumor limited your physical functioning today?*

- ☐ *Not at all*
- ☐ *A little*
- ☐ *Somewhat*
- ☐ *Severely*
- ☐ *Extremely*

***Patient Global Impression of Change in Symptoms – Stiffness***

***Please rate the change in your stiffness at the site of your tumor today compared to your stiffness at the site of your tumor before you received treatment at the start of the study.***

- ☐ *Much improved*
- ☐ *Moderately improved*
- ☐ *A little improved*
- ☐ *No change*
- ☐ *A little worse*
- ☐ *Moderately worse*
- ☐ *Much worse*

## 15.10. Surgical Assessment Questionnaire

**Table 15.1: Sample Surgical Assessment Questionnaire**

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

## 15.11. Employment status and productivity questions

Please choose one of the following which best describes your current work situation.

☐ Employed

☐ Self-employed

☐ Unemployed

☐ Student

☐ Retired

☐ Other, please specify: _____

If employed, self-employed or unemployed, which of the following best describes your current work situation?

☐ I am working full time for pay

☐ I am only working part-time for pay because of my tumour

☐ I am only working part-time for pay for reasons not related to my tumour

☐ I am not working for pay because of my tumour

☐ I am not working for pay for reasons not related to my tumour

If you are working, in the past 4 weeks, on average, how many days per week did you miss from work due to your tumour?

Include time when you were late getting to work, when you left work early, and time spent for doctors' visits and hospitalizations.

☐ Days (Please record to the nearest half day. If none, record 0.)

## 15.12. Healthcare Resource Use Questions

1. Has the subject been hospitalized in the past 4 weeks?

☐ Yes

☐ No

If Yes,

1a. What was the date of admission? ___/___/____ (DD/MM/YYYY)

1b. What was the date of discharge? ___/___/____ (DD/MM/YYYY)

1c. Was the hospitalization related to the subject's tumour?

☐ Yes

☐ No

1d. What was the reason/diagnosis for hospitalization?

Specify: _____

1e. What was the nature of the hospitalization? (Please tick one)

☐ Urgent/ Emergency

☐ Scheduled/Planned

☐ Prolongation of existing hospitalization

1f. Number of days spent in general ward: _____

1g. Number of days spent in intensive care unit (ICU)
(or equivalent units, e.g. cardiac care or high dependency unit): _____

1h. Did the subject have any additional hospitalizations in the past 4 weeks?

☐ Yes

☐ No

If Yes, repeat questions 1a to 1g. If No, proceed to question 2.

2. Did the subject have any Accident & Emergency (emergency room) visits that did not result in hospitalization in the past 4 weeks?

Number of visits: _____ (If none, record 0)

2a. For each A&E (ER) visit record the following:

Was the visit related to the subject's tumour?

□ Yes

□ No

## 15.13. Schedule of Events

**Table 15.2: Schedule of Events – Part 1 (Blinded, Placebo-controlled Phase)**

| **Procedure**[a] | **Day -42 to -1**[b] | **P1-C1D1** | **P1-C1D8 ± 2d** | **P1-C1D15 ± 2d** | **P1-C1D22 ± 2d** | **P1-C2D1 ± 2d** | **P1-C2D8 ± 2d** | **P1-C2D15 ± 2d** | **P1-C2D22 ± 2d** | **P1-C3D1 ± 7d** | **P1-C3D15 ± 7d** | **P1-C4D1 ± 7d** | **P1-C5D1 ± 7d** | **P1-C6D1 ± 7d** | **P1 Compl./ Early Term**[c] **± 7d** | **P1-28 Day Post Tx**[d] **± 7d** | **P1 End St/12 Week post-Tx ± 7d** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **Screen**[b] | **Week 1** | **Week 2** | **Week 3** | **Week 4** | **Week 5** | **Week 6** | **Week 7** | **Week 8** | **Week 9** | **Week 11** | **Week 13** | **Week 17** | **Week 21** | **Week 25** | **LD+28d** | **LD+12 Week / < new Tx**[e] |
| Informed consent | X | | | | | | | | | | | | | | | | |
| Demog. & medical history | X | | | | | | | | | | | | | | | | |
| Height, weight | X | | | | | | | | | | | | | | X[f] | X[f] | |
| Vital signs, incl. BP, pulse, temp. | X[g] | X | | X | | X | | | | X | | X | X | X | X | X | |
| Physical examination[h] | X | | | | | X | | | | | | X | | | X | X | |
| ECG[i] | X | X | | X | | | | | | | | | | | X | X | |
| ECHO or MUGA scanning[j] | X | | | | | | | | | | | X | | | X | X[k] | |
| Chemistry, hematology | X | X | | X[l] | | X | | | | X | | X | X | X | X | X | |
| Liver function tests[m] | X | X[m] | X[m] | X[m] | X[m] | X[m] | X[m] | X[m] | X[m] | X[m] | X[m] | X[m] | X[m] | X[m] | X[m] | X[m] | |
| Urinalysis | | X | | | | | | | | | | X | | | X | X | |
| Hepatitis panel | X | | | | | | | | | | | | | | | | |
| Coagulation tests[n] | | X | | | | | | | | | | | | | X | X | |

| **Procedure**[a] | **Day -42 to -1**[b] | **P1-C1D1** | **P1-C1D8 ± 2d** | **P1-C1D15 ± 2d** | **P1-C1D22 ± 2d** | **P1-C2D1 ± 2d** | **P1-C2D8 ± 2d** | **P1-C2D15 ± 2d** | **P1-C2D22 ± 2d** | **P1-C3D1 ± 7d** | **P1-C3D15 ± 7d** | **P1-C4D1 ± 7d** | **P1-C5D1 ± 7d** | **P1-C6D1 ± 7d** | **P1 Compl./ Early Term**[c] **± 7d** | **P1-28 Day Post Tx**[d] **± 7d** | **P1 End St/12 Week post-Tx ± 7d** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **Screen**[b] | **Week 1** | **Week 2** | **Week 3** | **Week 4** | **Week 5** | **Week 6** | **Week 7** | **Week 8** | **Week 9** | **Week 11** | **Week 13** | **Week 17** | **Week 21** | **Week 25** | **LD+28d** | **LD+12 Week / < new Tx**[e] |
| Hormone testing[o] | X | X | | | | | | | | | | | | | X | X | |
| BPI Worst Pain NRS[p, q] | X | X | | | | | | | | X | | | X | | X | X | |
| Worst Stiffness NRS item[p,q] | X | X | | | | | | | | X | | | X | | X | X | |
| Most disturbing Sx assessment | | X | | | | | | | | | | | | | | | |
| PROMIS Physical Function Scale[p] | X | X | | | | | | | | X | | | X | | X | X | |
| Global Rating of Concept item | | X | | | | | | | | X | | | X | | X | X | |
| EQ-5D-5L instrument[p] | | X | | | | | | | | X | | | X | | X | X | |
| Review completed outpatient PROs | | X | | | | | | | | X | | | X | | X | X | |
| Pt. Global Impress. of Change item | | | | | | | | | | | | | | | X | X | |
| MRI of the affected joint[r] | X | | | | | | | | | | | X | | | X | X | X |

| **Procedure**[a] | **Day -42 to -1**[b] | **P1-C1D1** | **P1-C1D8 ± 2d** | **P1-C1D15 ± 2d** | **P1-C1D22 ± 2d** | **P1-C2D1 ± 2d** | **P1-C2D8 ± 2d** | **P1-C2D15 ± 2d** | **P1-C2D22 ± 2d** | **P1-C3D1 ± 7d** | **P1-C3D15 ± 7d** | **P1-C4D1 ± 7d** | **P1-C5D1 ± 7d** | **P1-C6D1 ± 7d** | **P1 Compl./ Early Term**[c] **± 7d** | **P1-28 Day Post Tx**[d] **± 7d** | **P1 End St/12 Week post-Tx ± 7d** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **Screen**[b] | **Week 1** | **Week 2** | **Week 3** | **Week 4** | **Week 5** | **Week 6** | **Week 7** | **Week 8** | **Week 9** | **Week 11** | **Week 13** | **Week 17** | **Week 21** | **Week 25** | **LD+28d** | **LD+12 Week / < new Tx**[e] |
| Range-of-motion assessment[s] | X | | | | | | | | | | | X | | | X | X | |
| Serum pregnancy test[t] | X | | | | | X | | | | X | | X | X | X | X | X | X |
| Archival tumor tissue[u] | X | | | | | | | | | | | | | | | | |
| PK, PDy blood sampling[v] | | X | | X | | X | | | | X | | | X | | | | |
| Analgesic use assessment | X[w] | X | | | | | | | | X | | | X | | X | X | |
| Subject randomization | | X | | | | | | | | | | | | | | | |
| Dispense study Tx | | X | | X | | X | | | | X | | X | X | X | | | |
| In-clinic study Tx dosing[x] | | X | | X | | | | | | | | | | | | | |
| Study Tx dosing[y] | | —— Twice daily dosing through Week 24[y] —— | | | | | | | | | | | | | | | |
| Tx compliance assessment | | | | X | | X | | | | X | | X | X | X | X | | |
| Concomitant medications | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |

| **Procedure**[a] | **Day -42 to -1**[b] | **P1-C1D1** | **P1-C1D8 ± 2d** | **P1-C1D15 ± 2d** | **P1-C1D22 ± 2d** | **P1-C2D1 ± 2d** | **P1-C2D8 ± 2d** | **P1-C2D15 ± 2d** | **P1-C2D22 ± 2d** | **P1-C3D1 ± 7d** | **P1-C3D15 ± 7d** | **P1-C4D1 ± 7d** | **P1-C5D1 ± 7d** | **P1-C6D1 ± 7d** | **P1 Compl./ Early Term**[c] **± 7d** | **P1-28 Day Post Tx**[d] **± 7d** | **P1 End St/12 Week post-Tx ± 7d** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **Screen**[b] | **Week 1** | **Week 2** | **Week 3** | **Week 4** | **Week 5** | **Week 6** | **Week 7** | **Week 8** | **Week 9** | **Week 11** | **Week 13** | **Week 17** | **Week 21** | **Week 25** | **LD+28d** | **LD+12 Week / < new Tx**[e] |
| Adverse events[z] | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Surgical Assessment Questionnaire | X | | | | | | | | | | | | | | X | X | |
| Collection of surgical data[aa] | | | | | | | | | | | | | | | X[aa] | X[aa] | X[aa] |
| HCRU & productivity assessment | | X | | | | X | | | | X | | X | X | X | X | X | |
| PGx blood sampling[bb] | | | | | | | | | | | | | | | | | |

AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BP = blood pressure; BPI = Brief Pain Inventory; C = cycle; Compl = Completion; D/d = Day; Demog. = demographics; ECG = electrocardiogram; ECHO = echocardiography; End St./12 Week post Tx. = End-of-Study/12 Week Post-Treatment; EQ-5D-5L =EuroQol five-dimensional descriptive system; FSH = follicle-stimulating hormone; GCT-TS = giant cell tumor of the tendon sheath; GGT = gamma-glutamyl transpeptidase; HCRU = healthcare resource use; incl. = including; LD = last dose; LH = luteinizing hormone; MRI = magnetic resonance imaging; MUGA = multi-gated acquisition; NRS = numeric rating scale; P = Part; PDy = pharmacodynamic; PGx = pharmacogenomic; PK = pharmacokinetic; PRO = patient-reported outcome; PROMIS = Patient-reported Outcomes Measurement Information System; Pt = patient; PVNS = pigmented villonodular synovitis; Screen = Screening; Sx = symptom; temp. = temperature; Tx = treatment; Week = week

[a] Effective 30 Sep 2016, subjects who wish to continue onto the open label part of this study (Part 2) will be unblinded after completion of the end of Part 1 assessments (Part 1 Completion visit/Early Termination visit) and those on placebo will be discontinued and will not have the 28 Day Post-treatment and End-of-Study Visit assessments.

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

[c] The Part 1 Completion visit applies to subjects who are not continuing into Part 2. Those continuing into Part 2 will instead have the assessments indicated at P2-C1D1 (see Table 15.3). Effective 30 Sep 2016, subjects who wish to continue onto the open label part of this study (Part 2) will be unblinded after completion of the end of Part 1 assessments (Part 1 Completion visit/Early Termination visit) and those on placebo will be discontinued; subjects on pexidartinib in Part 1 may continue into Part 2 to continue to receive pexidartinib. Subjects who discontinue Part 1 early, should complete the end of Part 1 assessments (Part 1 Completion visit/Early Termination) at or before the time of their last treatment (MRI or range of motion assessments do not need to be repeated, if completed in the previous 28 days).

[d] As of 30 Sep 2016, subjects who wish to continue onto the open label part of this study (Part 2) will be unblinded after completion of the end of Part 1 assessments (Part 1 Completion visit/Early Termination visit) and those on placebo will be discontinued and will not need to complete the Part 1 28 Day Post-Treatment Visit and associated procedures. Subjects who exit the study with radiologic disease progression will undergo their last study evaluation 28 ± 7 days after their last dose of study treatment or before any new PVNS therapy, including surgery, whichever occurs first. Any planned new PVNS therapy, including the type of surgical procedure, will be recorded. Subjects who withdraw from the study with radiologic progression do not undergo a Part 1 End-of-Study/12 Week Post-Treatment MRI.

[e] Subjects who end their study participation with no radiologic disease progression will undergo post-treatment procedures 28 ± 7 days after their last dose of study treatment and a final MRI 12 weeks ± 7 days after their last dose of study treatment or before any new PVNS therapy, including surgery, whichever occurs first. The latter MRI need not be performed if new PVNS therapy starts within 4 weeks of the 28 Day Post-treatment Visit. Before or at the Part 1 End-of-Study/12 Week Post-Treatment Visit, plans for any new PVNS therapy will be obtained. (see Footnote aa) As of 30 Sep 2016, subjects who wish to continue onto the open label part of this study (Part 2) will be unblinded after completion of the end of Part 1 assessments (Part 1 Completion visit/Early Termination visit) and those on placebo will be discontinued and will not have the 28 Day Post-treatment and End-of-Study Visit assessments.

[f] Weight only.

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

[h] In the event of early withdrawal or if the subject completes Part 1 but does not enter Part 2, a physical examination is performed at the 28 Day Post-treatment Visit.

[i] A standard 12-lead ECG is performed prior to dosing. Subjects should be told not to take their morning dose of study treatment at home on days when an ECG is performed; instead, they should bring their study treatment bottle to the clinic and take their morning dose upon site instruction. At the P1-C1D1 and P1-C1D15 visits only, the ECG is performed before and 2 hours after dosing. The 2 hour post-dose ECG should begin within 10 minutes of the 2 hour post-dose time point.

[j] ECHO or MUGA scanning is chosen by Investigator preference. However, the same imaging platform must be used throughout the study.

[k] ECHO or MUGA scanning should only be repeated if more than 3 months have elapsed since the last procedure. Subjects who show a reduced ejection fraction relative to baseline at the last visit should be followed until a stable ejection fraction is measured by two consecutive tests.

[l] Hematology only.

[m] Alkaline phosphatase, ALT, AST, total and direct bilirubin, and GGT should be assessed at screening, weekly during P1-C1 beginning on Day 1, weekly during P1-C2 beginning on Day 1, biweekly during P1-C3 beginning on Day 1, and on Day 1 of every cycle thereafter. More frequent monitoring is required in the case of increased liver function tests (see Section 5.3).

[n] Subjects receiving concomitant warfarin should have their anti-coagulation status carefully monitored for any necessary dose adjustments (see Section 5.3).

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

[p] Subjects should record responses to the BPI Worst Pain NRS item, Worst Stiffness NRS item, PROMIS Physical Function Scale, and EQ-5D-5L in the eDiary before any invasive procedures. (NOTE: at the Screening Visit only, the recall period will be the preceding week for the BPI Worst Pain NRS item and Worst Stiffness NRS item. The subject's response must be documented in the medical notes.)

[q] Subjects should be reminded to complete the BPI Worst Pain NRS item and the Worst Stiffness NRS item, at least 4 of 7 consecutive days for 2 weeks prior to randomization, and prior to Day 1 of P1-C1, P1-C3, and P1-C5 and before the Part 1 Completion Visit (Week 25). In the event of early withdrawal or if the subject completes Part 1 but does not enter Part 2, this item will be completed prior to the 28 Day Post-treatment Visit.

[r] The Investigator may request a centrally read blinded MRI to confirm progression, eg, if a subject's mid-study clinical profile or local radiological assessment indicates progression.

[s] A range-of-motion assessment in the affected joint or tumor location will be performed by a blinded independent third party assessor.
[t] Women of childbearing potential must have a serum pregnancy test within 14 days of randomization (or, where different regulations apply, within 72 hours of randomization). (Women who have documentation of at least 12 months of spontaneous amenorrhea and have an FSH level > 40 mIU/mL will be considered postmenopausal and need not undergo pregnancy testing.)
[u] Archival surgical tissue from PVNS/GCT-TS tumors should be obtained at screening (or whenever available) for biomarker assessment.
[v] Details on blood sampling are found in Section 6.4.16 (PK) and Section 6.4.15 (PDy).
[w] A diary of analgesic use must be kept for the 2-week period before the first dose of study treatment.
[x] The morning dose of study treatment should be administered in the clinic on the days indicated; P1-C1D1 should be within 3 days after randomization.
[y] Dose administration by the subject at home. See Section 3.1 for dose reduction as of P1-C1D15. Subjects should take their last dose of study treatment the evening before their scheduled Part 1 Completion Visit (Week 25).
[z] After the subject provides signed informed consent; AEs are monitored throughout the study via safety assessments, observation, and subject reporting (see Section 6.4.17).
[aa] If surgical resection of the tumor is performed within 12 weeks after the last dose of study treatment, details of the surgery and its outcome should be obtained (see Table 15.4). After completion of the end of Part 1 assessments (Part 1 Completion visit/Early Termination visit), subjects who wish to continue onto the open label part of this study (Part 2) will be unblinded and those on placebo will be discontinued and will not need to have surgical data follow-up.
[bb] The pharmacogenomics blood sample is optional. If taken, it should only be taken once as soon as reasonably possible after the subject has signed the consent form.

**Table 15.3: Schedule of Events – Part 2 (Open-label Phase)**

| | **P2-C1D1**[a] | **P2-C1D8 ± 2d** | **P2-C1D15 ± 2d** | **P2-C1D22 ± 2d** | **P2-C2D1 ± 2d** | **P2-C2D8 ± 2d** | **P2-C2D15 ± 2d** | **P2-C2D22 ± 2d** | **P2-C3D1 ± 7d** | **P2-C3D15 ± 7d** | **P2-C4D1 ± 7d** | **P2-C5D1 ± 7d** | **P2-C6D1 ± 7d** | **P2-C7D1 ± 7d** | **P2-C10+D1**[b] **± 7d** | **P2-Post Tx**[c] **± 7d** | **End St./ Ear. Term. ± 7d** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Procedure**[d] | **Week 25** | **Week 26** | **Week 27** | **Week 28** | **Week 29** | Week 30 | **Week 31** | Week 32 | **Week 33** | Week 35 | **Week 37** | **Week 41** | **Week 45** | **Week 49** | **Week 61+** | **LD + 28d** | **LD + 12 Week/ < new Tx**[e] |
| Weight | X | | | | | | | | | | | | | | | X | |
| Vital signs, incl. BP, pulse, temp. | X | | X | | X | | | | X | | X | X[f] | X[f] | X[f] | X[f] | X[f] | |
| Physical examination | X | | | | X | | | | | | X | | | X | X | X[f] | |
| ECG | X[g] | | X[g] | | | | | | | | | | | X | | X | |
| ECHO or MUGA scanning | X | | | | | | | | | | X | | | X | | X[h] | |
| Chemistry, hematology | X | | X[i] | | X | | | | X | | X[f] | X[f] | X[f] | X[f] | X[f] | X[f] | |
| Liver function tests[j] | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | |
| Urinalysis | X | | | | | | | | | | X | | | | | X | |
| Coagulation tests[k] | X | | | | | | | | | | | | | | | X | |
| Hormone testing[l] | X | | | | | | | | | | | | | X | | X | |
| BPI Worst Pain NRS item | X | | | | | | | | | | X[f,m] | | | X[f,m] | X[f,m] | X[f,m] | |
| Worst Stiffness NRS item | X | | | | | | | | | | X[f,m] | | | X[f,m] | X[f,m] | X[f,m] | |

| | **P2-C1D1**[a] | **P2-C1D8 ± 2d** | **P2-C1D15 ± 2d** | **P2-C1D22 ± 2d** | **P2-C2D1 ± 2d** | **P2-C2D8 ± 2d** | **P2-C2D15 ± 2d** | **P2-C2D22 ± 2d** | **P2-C3D1 ± 7d** | **P2-C3D15 ± 7d** | **P2-C4D1 ± 7d** | **P2-C5D1 ± 7d** | **P2-C6D1 ± 7d** | **P2-C7D1 ± 7d** | **P2-C10+D1**[b] **± 7d** | **P2-Post Tx**[c] **± 7d** | **End St./ Ear. Term. ± 7d** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Procedure**[d] | **Week 25** | **Week 26** | **Week 27** | **Week 28** | **Week 29** | Week 30 | **Week 31** | Week 32 | **Week 33** | Week 35 | **Week 37** | **Week 41** | **Week 45** | **Week 49** | **Week 61+** | **LD + 28d** | **LD + 12 Week/ < new Tx**[e] |
| PROMIS Physical Function Scale | X | | | | | | | | | | X[f] | | | X[f] | X[f] | X[f] | |
| EQ-5D-5L instrument | X | | | | | | | | | | X[f] | | | X[f] | X[f] | X[f] | |
| Review completed outpatient PROs | X | | | | | | | | | | X | | | X | X | X | |
| MRI of the affected joint[n] | X | | | | | | | | | | X[f] | | | X[f] | X[f] | X[f] | X[o] |
| Range-of-motion assessment[p] | X | | | | | | | | | | X[f] | | | X[f] | X[f] | X[f] | |
| Serum pregnancy test | X | | | | X | | | | X | | X | X | X | X | X | X | X |
| PK, PDy blood sampling[q] | X | | X | | X | | | | | | | | | | | | |
| Analgesic use assessment | X | | | | | | | | | | X | | | X | X | X | |
| Dispense pexidartinib | X | | | | X | | | | X | | X | X | X | X | X | | |
| In-clinic pexidartinib dosing[r] | X | | X | | | | | | | | | | | X | | | |
| Pexidartinib dosing[s] | X | —— Twice daily dosing[s] —— | | | | | | | | | | | | | | | |

| | **P2-C1D1**[a] | **P2-C1D8 ± 2d** | **P2-C1D15 ± 2d** | **P2-C1D22 ± 2d** | **P2-C2D1 ± 2d** | **P2-C2D8 ± 2d** | **P2-C2D15 ± 2d** | **P2-C2D22 ± 2d** | **P2-C3D1 ± 7d** | **P2-C3D15 ± 7d** | **P2-C4D1 ± 7d** | **P2-C5D1 ± 7d** | **P2-C6D1 ± 7d** | **P2-C7D1 ± 7d** | **P2-C10+D1**[b] **± 7d** | **P2-Post Tx**[c] **± 7d** | **End St./ Ear. Term. ± 7d** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Procedure**[d] | **Week 25** | **Week 26** | **Week 27** | **Week 28** | **Week 29** | Week 30 | **Week 31** | Week 32 | **Week 33** | Week 35 | **Week 37** | **Week 41** | **Week 45** | **Week 49** | **Week 61+** | **LD + 28d** | **LD + 12 Week/ < new Tx**[e] |
| Tx compliance assessment | X | | X | | X | | | | X | | X | X | X | X | X | X | |
| Concomitant medications | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Adverse events[t] | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Surgical Assessment Questionnaire | X | | | | | | | | | | | | | X | | X | |
| Collection of surgical data[u] | | | | | | | | | | | | | | X[u] | | X[u] | X[u] |
| PGx blood sampling[v] | | | | | | | | | | | | | | | | | |

AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BP = blood pressure; BPI = Brief Pain Inventory; C = cycle; D/d = Day; ECG = electrocardiogram; ECHO = echocardiography; End St./Ear. Term. = End-of-Study/Early Termination; EQ-5D-5L =EuroQol five-dimensional descriptive system; FSH = follicle-stimulating hormone; GGT = gamma-glutamyl transpeptidase; incl. = including; LD = last dose; LH = luteinizing hormone; MRI = magnetic resonance imaging; MUGA = multi-gated acquisition; NRS = numeric rating scale; P = Part; PDy = pharmacodynamic; PGx = pharmacogenomic; PK = pharmacokinetic; PRO = patient-reported outcome; PROMIS = Patient-reported Outcomes Measurement Information System; PVNS = pigmented villonodular synovitis; temp. = temperature; Tx = treatment; Week = week

[a] The Part 1 Completion (Week 25) Visit will serve as the first visit of Part 2 and will be designated as P2-C1D1. All procedures listed for this visit are for reference only and will already have been conducted at the Part 1 Completion (Week 25) Visit except for the following, which should be performed at this visit: (i) administering the morning dose of pexidartinib; (ii) dispensing the dosing diary; (iii) 2-hour post-dose ECG; and (iv) dispensing the analgesic use diary.

[b] Starting with P2-C10 (Week 61), subjects will return to the clinic every 12 weeks (ie, P2-C13, P2-C16, etc.) to undergo the procedures indicated.

[c] If the subject withdraws before completing Part 2 or completes Part 2 but declines to continue treatment for study of longer efficacy and safety follow-up or in the separate continuation study, the post-treatment procedures should be completed 28 ± 7 days after the last dose of study treatment and before initiating any new PVNS therapy, including surgery. Subjects who complete Part 2 without experiencing progression or intolerability, or subjects who undergo surgical resection of their tumor after study treatment will be eligible to continue for longer efficacy and safety follow-up or to enter a separate protocol to continue receiving pexidartinib or for surgical data collection.. Subjects who enter the separate protocol will not undergo Post-treatment and End-of-Study Visits.

[d] Effective 30 Sep 2016, subjects who wish to continue onto the open label part of this study (Part 2) will be unblinded after completion of the end of Part 1 assessments (Part 1 Completion visit/Early Termination visit) and those on placebo will be discontinued; subjects on pexidartinib in Part 1 may continue into Part 2 to continue to receive pexidartinib. If the patient is known to have been on pexidartinib treatment in Part 1, then visits and associated procedures are only required on Day 1 of each cycle in Part 2.

[e] The End-of-Study/Early Termination MRI need not be performed if new PVNS therapy begins within 4 weeks of the Post-treatment Visit. Before or at the End-of-Study/Early Termination Visit, plans for any new PVNS therapy will be obtained. Details of any surgical treatment will be obtained per Footnote u.

[f] A physical examination by study staff, MRI, blinded range-of-motion assessment of the joint location by a third-party examiner not otherwise affiliated with the trial, and administration of the PRO instruments are performed at all of the indicated visits including the P2-C4D1 visit, every 12 weeks thereafter (ie, P2-C7D1, P2-C10D1, etc.), and at the Post-treatment Visit. Vital sign assessment, clinical laboratory studies (chemistry, hematology), and PK/PDy blood sampling will be performed at all of the indicated visits, including the P2-C4D1 visit, every 12 weeks thereafter (ie, P2-C7D1, P2-C10D1, etc.), P2-C5D1, and P2-C6D1. [NOTE: On study visit days, the PRO instruments, including the EQ-5D-5L, should be administered before performing any invasive procedures.]

[g] A standard 12-lead ECG is performed 2 hours after dosing at the P2-C1D1 visit and before and 2 hours after dosing at the P2-C1D15 visit. The 2-hour post-dose ECG measurements should begin within 10 minutes of the 2 hour post-dose time point. Thereafter, the ECG and blood draw for hormone testing is performed before dosing at the C13D1 visit, every 24 weeks thereafter (ie, C19D1, C25D1, etc.), and at the Post-treatment Visit.

[h] ECHO or MUGA scanning should only be repeated if more than 3 months have elapsed since the last procedure. Subjects who show a reduced ejection fraction relative to baseline at the last visit should be followed until a stable ejection fraction is measured by two consecutive tests.

[i] Hematology only.

[j] Alkaline phosphatase, ALT, AST, total and direct bilirubin, and GGT should be assessed weekly during P2-C1 beginning on Day 1, weekly during P2-C2 beginning on Day 1, biweekly during P2-C3 beginning on Day 1, and on Day 1 of every cycle thereafter. More frequent monitoring is required in the case of increased liver function tests (see Section 5.3).

[k] Subjects receiving concomitant warfarin should have their anti-coagulation status carefully monitored for any necessary dose adjustments (see Section 5.3) .

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

[m] Subjects should be reminded to complete the BPI Worst Pain NRS item and Worst Stiffness NRS item for at least 4 of 7 consecutive days prior to Day 1 of P2-C4, P2-C7, P2-C10, and before the Post-treatment Visit.

[n] The investigator may request a centrally read MRI to confirm progression as detailed in the Imaging Charter.

[o] For subjects who discontinue the study before completing Part 2 or complete Part 2 but decline to continue treatment for study of longer efficacy and safety follow-up or to enter the separate continuation study for reasons other than progression, the end-of-study or early termination MRI should be completed 12 weeks ± 7 days after the last dose of study treatment or before starting any new PVNS therapy, including surgery, whichever occurs first. Subjects who withdraw from the study with progression do not undergo an End-of-Study/Early Termination MRI.

[p] A range-of-motion assessment in the affected joint or tumor location will be performed by a blinded independent third party assessor.

[q] Details on blood sampling are found in Section 6.4.16 (PK) and Section 6.4.15 (PDy).

[r] The morning dose of pexidartinib should be administered in the clinic at all of the indicated time points.

[s] Dose administration by the subject at home.

[t] AEs are monitored throughout the study via safety assessments, observation, and subject reporting (see Section 6.4.17).

[u] If surgical resection of the tumor is performed within 12 weeks after the last dose of study treatment, details of the surgery and its outcome should be obtained (see Table 15.4).

[v] The pharmacogenomic blood sample is optional. If taken, it should only be taken once as soon as reasonably possible after the subject has signed the consent form.

## Table 15.4: Schedule of Events – For Subjects Who Undergo Surgical Resection

| | Follow Up Visit 1 | | Follow Up Visit 2 | Follow Up Contact 1 | Follow Up Contact 2 | Follow Up Contact 3 | Follow Up Contact 4 |
|---|---|---|---|---|---|---|---|
| **Procedure[a]** | **Within 4 Weeks prior to Surgery** | **During or Shortly after Surgery** | **4 months (+/- 2 weeks) after Surgery** | **8 months (+/- 2 weeks) after Surgery** | **12 months (+/- 2 weeks) after Surgery** | **18 months (+/- 2 weeks) after Surgery** | **24 months (+/- 2 weeks) after Surgery** |
| BPI Worst Pain NRS | X[b] | | X | | | | |
| Worst Stiffness NRS item | X[b] | | X | | | | |
| PROMIS Physical Function Scale | X[b] | | X | | | | |
| MRI of the affected joint | X[c] | | X | | | | |
| Range-of-motion assessment | X[b] | | X | | | | |
| Reasons of Surgery | X[b] | | | | | | |
| Blood Chemistry, Hematology | X[d] | | | | | | |
| Liver function tests | X[d] | | | | | | |
| Coagulation tests | X[d] | | | | | | |
| Urinalysis | X[d] | | | | | | |
| Serum pregnancy test | X[d] | | | | | | |
| ECG | X[d] | | | | | | |
| Surgical Procedure and Findings[e] | | X | | | | | |
| Surgical Complications | | | X | | | | |
| Tumor Sample Submission | | X | | | | | |
| Collection of serious adverse events | X | | X | | | | |
| Disease Recurrence[f] | | | X | X | X | X | X |
| End of Study CRF Completion | | | | | | | X |
| PGx blood sampling[g] | | | | | | | |

BPI = Brief Pain Inventory; CRF = Case report form; ECG = electrocardiogram; MRI = magnetic resonance imaging; NRS = numeric rating scale; PGx = pharmacogenomic; PROMIS = Patient-reported Outcomes Measurement Information System; TGCT = tenosynovial giant cell tumor

[a] If a subject has surgery within 4 weeks of the last dose of study treatment, the subject does not need to have the Post-Treatment Visit evaluations (in Table 15.2 and Table 15.3), but will need to have the safety lab tests (blood chemistry, hematology, liver function tests, coagulation tests, urinalysis, and serum pregnancy test) and an ECG performed at least 7 days after the

last dose of study treatment, but prior to surgery. However, if a subject has surgery after 4 weeks of the last dose of study treatment, the subject should have the Post-Treatment Visit evaluations (in Table 15.2 and Table 15.3). None of these subjects need to have the End-of-Study Visit (in Table 15.2 and Table 15.3).

[b] Only perform if not done within 4 weeks prior to the surgery.

[c] Only perform if not done within 12 weeks prior to the surgery.

[d] Only for subjects who have surgery within 4 weeks of the last dose of study treatment.

[e] Including planned surgical procedure and actual surgical procedure performed, surgical margin, copies of surgical report and pathology report, if available .

[f] Disease recurrence is defined as the need for any new therapeutic intervention of TGCT. Such follow-up can be performed via phone contact with the subject.

[g] The pharmacogenomic blood sample is optional. If taken, it should only be taken once as soon as reasonably possible after the subject has signed the consent form.