CLINICAL STUDY PROTOCOL

Title	A Phase 1 Study to Assess Safety, Pharmacokinetics, and Pharmacodynamics of PLX3397 in Patients with Advanced, Incurable, Solid Tumors in which the Target Kinases Are Linked to Disease Pathophysiology
Protocol Number	PLX108-01
IND Number	105,521
Sponsor	Plexxikon Inc. 91 Bolivar Drive Berkeley, CA 94710, USA
Medical Monitor	PPD Plexxikon Inc. 91 Bolivar Drive Berkeley, CA 94710, USA PPD
Date/Version	25 February 2020/Amendment 12

Confidentiality Statement

1.0 SPONSOR SIGNATURE

I have read and approved this protocol.

PPD

Medical Monitor/Regional Director Signature

25 FEB 2020.

Date of Signature
(DD Mmm YYYY)

PPD

Medical Monitor/Regional Director Name (print)

2.0 INVESTIGATOR SIGNATURE

I have read and approved this protocol. My signature, in conjunction with the signature of the Sponsor, confirms the agreement of both parties that the clinical study will be conducted in accordance with the protocol and all applicable laws and regulations including, but not limited to, the International Conference on Harmonisation Guideline for Good Clinical Practice (GCP), the Code of Federal Regulations (CFR), and the ethical principles that have their origins in the Declaration of Helsinki.

Nothing in this document is intended to limit the authority of a physician to provide emergency medical care under applicable regulations.

Investigator Signature

Date of Signature
(DD Mmm YYYY)

Investigator Name and Title (print)

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3.0 CONTACTS

3.1 Emergency and Safety Contacts

Medical Monitor:

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Address: 91 Bolivar Drive
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PPD

SAE/Safety Monitoring Contact:

Plexxikon Safety Inbox
PPD

4.0 LIST OF ABBREVIATIONS

Abbreviation or Term[a]	Definition/Explanation
AE	Adverse event
ALT	Alanine aminotransferase
APTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
ATC	Anaplastic thyroid carcinoma
$AUC_{0-\infty}$	Area under the concentration-time curve from time zero extrapolated to infinite time
AUC_{0-t}	Area under the concentration-time curve from time zero to the time of the last quantifiable concentration
AV	Atrioventricular
β-HCG	Beta-human chorionic gonadotropin
BAP	Bone-specific alkaline phosphatase
BID	Twice daily
BMI	Body mass index
BP	Blood pressure
BUN	Blood urea nitrogen
Ca^{++}	Calcium
CBC	Complete blood count
CEA	Carcinoembryonic antigen
CFR	Code of Federal Regulations
CHF	Congestive heart failure
CI	Confidence interval
Cl-	Chloride
CL_{cr}	Creatinine clearance
CL_T	Total body clearance
CL/F	Apparent oral clearance
C_{max}	Maximum observed concentration
C_{min}	Trough observed concentration
CNS	Central nervous system
CPE	Clinical Planned Event
CRF	Case report form
CRP	C-reactive protein
CTA	Clinical Trial Agreement
CTCs	Circulating Tumor Cells
CTCAE	Common Toxicity Criteria for Adverse Events
CTX	C-telopeptide of type I collagen
CTX-II	C-telopeptide of type II collagen
CV	Coefficient of variation
CYP	Cytochrome P450
DB	Direct bilirubin
D/C	Discontinue

Abbreviation or Term[a]	Definition/Explanation
ECOG	Eastern Cooperative Oncology Group
ECG	Electrocardiogram
Eg	Exempli gratia (for example)
ESR	Erythrocyte sedimentation rate
F	Bioavailability
FACS	Fluorescence Activated Cell Sorting
FDA	Food and Drug Administration
GC	Gas chromatography
GCP	Good Clinical Practice
GFR	Glomerular filtration rate
GGT	Gamma glutamyl transferase
GIST	Gastrointestinal stromal tumor
GLP	Good laboratory practice
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCO_3^-	Bicarbonate
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HNSTD	Highest non-severely toxic dose
HPF	High-power field
HPLC	High-performance liquid chromatography
HR	Heart rate
hr	Hour or hours
IB	Investigator's brochure
Ie	Id est (that is)
IEC	Independent ethics committee
IL-1β	Interleukin-1β
IL-6	Interleukin-6
INR	International normalized ratio
IRB	Institutional review board
IU	International unit
IV	Intravenous, intravenously
LDH	Lactate dehydrogenase
LC	Liquid chromatography
MedRA	Medical Dictionary for Drug Regulatory Activities
MIC	Minimum inhibitory concentration
MMP-3	Matrix metallopeptidase-3
MRSD	Maximum recommended starting dose
MRT	Mean residence time
MS	Mass spectrometry
MTD	Maximum tolerated dose

Abbreviation or Term[a]	Definition/Explanation
NOAEL	No-observed-adverse-effect level
NOEL	No-observed-effect-level
NTX	N-telopeptide of type I collagen
NRS	Numeric Rating Scale
P1NP	Procollagen type I intact N-terminal propeptide
PCI	Potential clinical importance
PD	Pharmacodynamic(s)
PK	Pharmacokinetic(s)
PO	Per os (administered by mouth)
PRO	Patient reported outcome
PT	Prothrombin time
PTT	Partial thromboplastin time
PVNS	Pigmented villonodular synovitis
QC	Quality control
QTcF	QT corrected Fridericia
RP2D	Recommended Phase 2 dose
RBC	Red blood cell
SAE	Serious adverse event
SD	Standard deviation
STD	Severely toxic dose
$t_{1/2}$	Terminal elimination half-life
T_3	Triiodothyronine
T_4	Thyroxine
t_{max}	Time of maximum observed concentration
TAM	Tumor-associated macrophage
TB	Total bilirubin
TEAE	Treatment-emergent adverse event
TRAP 5b	Tartrate-resistant acid phosphatase
TSH	Thyroid-stimulating hormone
UGT	uridine diphosphate glucuronosyltransferase
ULN	Upper limit of normal
UV	Ultraviolet
WBC	White blood cell
WOCBP	Women of childbearing potential
WOMAC	Western Ontario and McMaster Universities Osteoarthritis Index

[a] All of these abbreviations may or may not be used in protocol.

5.0 SYNOPSIS

Title	A Phase 1 Study to Assess Safety, Pharmacokinetics, and Pharmacodynamics of PLX3397 in Patients with Advanced, Incurable, Solid Tumors in which the Target Kinases Are Linked to Disease Pathophysiology
Study Objective(s)	PLX3397 (hereafter referred to by its generic name pexidartinib) is a selective inhibitor of Fms, Kit, and oncogenic Flt3 kinase activity. The primary objective of this study is to evaluate the safety and pharmacokinetics of orally administered pexidartinib in patients with advanced, incurable, solid tumors in which these target kinases are linked to disease pathophysiology. The proliferation and metastasis of a number of tumors are driven in part by Flt3, Kit, or Fms activity. These tumors include, but are not limited to, gastrointestinal stromal tumor and melanoma (Kit); glioma, breast cancer, prostate cancer, multiple myeloma, and osteosarcoma (Fms/CSF-1). The secondary objective is to measure the pharmacodynamic activity of pexidartinib via blood, plasma and urine biomarkers of Fms activity.
Study Design	Open-label, sequential dose escalation design. Once the recommended phase 2 dose (RP2D) is reached, an additional six extension cohorts will be opened.
Number of Patients	Enrollment in the dose escalation phase is planned to include up to 50 patients (depending on the number of dose escalation cohorts required) to evaluate pharmacokinetics and observed toxicity. Approximately 70 patients are planned to be enrolled in six extension cohorts with the possibility of 30 additional patients in a specific cohort if necessary (Section 24.6).
Study Procedures	After providing informed consent, patients will undergo screening for eligibility to participate in the study. Screening will start within 21 days prior to dosing with the exception of tumor burden assessment (e.g., CT scan) which may have been performed within 28 days. A cycle of dosing is defined as 28 days. In each dose escalation cohort, patients will receive their assigned dose of pexidartinib on the morning of Cycle 1 Day 1 (C1D1) and will remain in the outpatient clinic for 8 hours for observation and pharmacokinetic (PK) sampling. For QD dosing, PK samples will be collected prior to dosing and 0.5, 1, 2, 4, and 8 hours following dosing. The initial dosing regimen of pexidartinib will be once daily by oral administration. A twice daily dosing regimen may be used in subsequent cohorts, depending on the PK data obtained from once-daily dosing in the first cohort. For BID dosing, PK samples will be obtained predose (AM) and 1, 2, 4, 7 hours postdose on C1D1. The second dose will then be administered, and a 1 hr post dose sample will be obtained (8 hours after the first dose). Patients will return to the clinic on the morning of C1D2 and C1D8 prior to dosing on that day for evaluation and blood draw to obtain the predose PK time-point (approximately 12 hours after the previous evening dose for a BID dosing regimen). Patients will continue to dose pexidartinib once or twice daily and return to the clinic for evaluation on C1D8. On C1D15 and C1D16 (±2 days), blood samples will be obtained once again for measurement of pexidartinib PK, using the same sampling times as on C1D1 and C1D2. Patients will return to the clinic on C2D1 for evaluation. If pexidartinib has been well tolerated and there has been no clinical evidence of disease progression, continued dosing will be permitted. Patients with solid tumors will be monitored for response and disease progression with tumor burden assessments every two months. In selected cohorts, 3–6 patients will be treated with a pexidartinib dose of 100 mg QD during a one-week run-in period before increasing to the full dose for that cohort, in order to profile the pharmacodynamic (PD) dose response activity of pexidartinib at doses below 300 mg QD. Similarly, 3–6 patients will be treated with a pexidartinib dose of 200 mg QD during a one-week run-in period. After baseline predose blood is obtained on C1D(-7), the first dose of 100 mg or 200 mg will be administered, and PK samples will be obtained. Patients will return to the clinic the following AM (C1D(-6)) and 2 days later (C1D(-4)) for blood draws for PK and the PD biomarkers. They will then return for C1D1 for initiation of dosing at the full dose for that cohort.

	At the recommended Phase 2 dose (RP2D), a total of six Extension cohorts of approximately 10 patients each (except for the miscellaneous cohort, which will include up to approximately 20 patients) will be enrolled and followed for safety and tumor response as assessed by radiographic imaging. These six cohorts consist of 1) mucoepidermal carcinoma (MEC) of the salivary gland, 2) pigmented villo-nodular synovitis (PVNS), 3) GIST, 4) anaplastic thyroid carcinoma (ATC), 5) solid tumors with documented malignant pleural or peritoneal effusions, and 6) miscellaneous tumor types for which a scientific rationale exists for treatment with pexidartinib. For PVNS patients, imaging will also be performed approximately 30 days and 12 weeks after last study drug. Patients will be monitored throughout the study for adverse reactions to the drug formulation and/or study procedures. For the dose escalation cohorts, clinical laboratory assessments (hematology, chemistry, and urinalysis) will be performed at screening, C1D8, C1D15, and at the beginning of each subsequent 28 day cycle for those patients who continue on therapy, and at study completion or upon early withdrawal. Urinary, blood and serum biomarkers of response will be evaluated on C1D1, C1D8, and C2D1. Blood pressure, respiratory rate, pulse, and temperature will be measured at screening and predose at each study visit except for C1D2 and C1D16. Blood pressure and pulse will also be monitored at 1 and 4 hours postdose on C1D1. Triplicate ECGs (within 2 minutes apart) will be obtained at screening, prior to dosing on C1D1, and at 2, 4, and 6 hours postdose on C1D1 and C1D15. A physical examination will be performed for each patient at screening, C1D8, C1D15, C2D1, and then monthly while continuing study drug administration, and at study completion or upon early withdrawal. For the Extension cohorts, a simplified study plan will be used, as detailed in the study flow chart. Patients enrolled after the implementation of Amendment 8 will complete two patient reported outcome (PRO) instruments: the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC®) and the Numeric Rating Scale (NRS) for PVNS Symptoms questionnaire. These will be completed predose at the clinic on C1D1, C1D15, C2D1, and monthly thereafter while continuing study drug administration, and at the End of Study visit. In addition, these patients will complete the NRS for PVNS Symptoms questionnaire on an outpatient basis for 6 consecutive days (Day -6 to Day -1) prior to each monthly clinic visit on C1D1, C2D1, C3D1, etc. while continuing study drug administration. The visit schedule for extension patients will be changed to every 12 weeks/3 cycles (with an option to complete on-site visits every 24 weeks/6 cycles if local safety laboratory testing and telephone check-ins are completed 12 weeks after each on-site visit) after a subject has completed at least C40 and if there are no ongoing safety or treatment issues. Imaging will be performed every 24 weeks/6 cycles, and PK, Urinalysis, and ECOG will be discontinued.
Key Patient Selection Criteria	**Inclusion** 1. Male or female patients ≥18 years old 2. For the dose escalation cohorts, patients with advanced, incurable, solid malignancies in which the target kinases are thought to be linked to disease pathophysiology and whose cancers are confirmed histologically. The tumors must fulfill BOTH of the following criteria: a) refractory to standard therapy, OR standard or curative therapy does not exist or is not considered appropriate by the investigator, AND b) tumor proliferation or metastasis could be driven or promoted in part by Flt3, Kit, or Fms/CSF-1 activity. 3. For the Extension cohorts, patients must have measurable disease by RECIST criteria and meet the following disease-specific criteria:

a. For advanced or recurrent MEC of the salivary gland, patients must not be candidates for curative surgery or radiotherapy.

b. For PVNS (including tenosynovial giant cell tumor), patients must have a histologically confirmed diagnosis of inoperable progressive or relapsing PVNS, or resectable tumor requiring mutilating surgery, as well as demonstrated progressive disease in the last 12 months.

c. For GIST, patients must have failed previous therapy with imatinib and sunitinib. Patients with known PDGFR mutations are excluded, but mutation testing is not required for study entry.

d. For ATC, patients must have histologically or cytologically diagnosed advanced ATC.

e. For metastatic solid tumors with documented malignant pleural, pericardial, and/or peritoneal effusions, patients must not be receiving specific therapy for the effusion (other than periodic drainage by needle) or have an indwelling drain.

f. Other solid tumor types can be included in a miscellaneous cohort, provided there is a clear scientific rationale for treatment with pexidartinib and upon approval by the Medical Monitor.

4. Women of child-bearing potential must have a negative pregnancy test within 7 days of initiation of dosing and must agree to use an acceptable non-hormonal method of birth control from the time of the negative pregnancy test for one month after the last dose of study drug. Highly effective non-hormonal methods of contraception include: intra-uterine device (non-hormonal), bilateral tubal occlusion, vasectomy, sexual abstinence, or barrier methods (e.g., condom, diaphragm). Women of non-childbearing potential may be included if they are either surgically sterile or have been postmenopausal for ≥1 year. Fertile men must also agree to use an acceptable method of birth control while on study drug and for one month after the last dose of study drug.
5. All associated toxicity from previous or concurrent cancer therapy must be resolved (to ≤Grade 1 or Baseline) prior to administration of pexidartinib.
6. Willing and able to provide written informed consent prior to any study related procedures and to comply with all study requirements.
7. ECOG performance status 0 or 1.
8. Life expectancy ≥3 months.
9. Adequate hematologic, hepatic, and renal function (absolute neutrophil count ≥1.5 x 10^9/L, Hgb >9 g/dL, platelet count ≥100 x 10^9/L, AST/ALT ≤2.5 x ULN or <5 x ULN in the presence of liver metastases, albumin ≥3 g/dL, creatinine ≤1.5 x ULN or calculated CrCl >60 mL/min using Cockcroft-Gault formula).

Exclusion

1. Specific anti-cancer therapy within 3 weeks prior to study drug administration.
2. Investigational drug use within 28 days of the first dose of pexidartinib.
3. Uncontrolled intercurrent illness.
4. Refractory nausea and vomiting, malabsorption, external biliary shunt, or significant small bowel resection that would preclude adequate absorption.
5. QTcF ≥450 msec (for males) or ≥470 msec (for females) at screening.
6. The presence of a medical or psychiatric condition that, in the opinion of the Principal Investigator, makes the patient inappropriate for inclusion in this study.

Duration of Study	The duration of the study is contingent on the number of dose levels in the dose escalation phase. Each dose escalation cohort will take approximately 6 weeks (7 weeks for cohorts with a one-week run-in period), including 2 weeks of recruitment. The PK analysis and MTD determination will be limited to the first 28 days of drug administration. Safety and response assessments will continue for the duration of drug administration for patients who continue study drug administration beyond 28 days. For the Extension cohorts, patients will be treated with study drug until progression or toxicity, until the phase 4 PVNS continuation study has been opened. Upon study termination, patients that don't transition to the phase 4 continuation study will be provided information regarding potential transition to commercial drug.
Dosage and Regimen	The proposed starting dose is 200 mg QD. A BID dosing regimen may be used in subsequent cohorts, pending review of the PK from the initial cohort. Cohorts of patients with solid tumors will be enrolled using 100% dose increments in the absence of drug-attributable Grade 2 toxicity. In each cohort (and following the one-week run-in period for applicable patients), the first patient will be observed for at least one week before additional patients in that cohort are treated with pexidartinib. Following the one-week run-in period for applicable patients, upon the occurrence of Grade 2 or greater drug-attributable toxicity, in the absence of dose limiting toxicity (DLT), dose escalation will proceed sequentially by 50% increments. From that point forward, the standard "3+3" design will be used. Following the one-week run-in period for applicable patients, if DLT is observed in one patient at a given cohort, at least 6 patients will be treated at that dose. Following the one-week run-in period for applicable patients, if DLT is observed in 2 or more of 6 patients at a dose level, then the next lower dose level will be expanded or an intermediate dose level will be introduced. The MTD is defined as the dose at which ≤1 of 6 patients experience a DLT during Cycle 1, with the next higher dose having at least 2 of the up to 6 patients experiencing a DLT during Cycle 1. If no DLT is observed, the recommended dose for further evaluation will be established based on toxicity, PK, and convenience of dosing in approximately 3–6 patients treated at that dose. Dose escalation will only be permitted if adequate safety and tolerability have been demonstrated at the previous lower dose for 28 days. The dosage for the Extension cohorts will be the RP2D level of 1000 mg/day, using a BID regimen.
Stopping Rules	For the dose escalation cohorts, two patients in any cohort of 6 patients with any of the following Dose Limiting Toxicities during the first 28 days of pexidartinib administration: • Any CTCAE (version 4) Grade 4 toxicity (Grade 4 neutropenia for ≥3 days) • Any CTCAE Grade 3 toxicity other than Grade 3 lymphopenia • CTCAE Grade 2 vomiting within two hours of drug administration on 3 consecutive days despite optimal anti-emetic therapy • If, for any reason, either the Principal Investigator or Sponsor deems further dose escalation inappropriate For the Extension cohorts, detailed guidance is provided in the protocol body for dose reduction criteria and discontinuation of therapy due to safety concerns.
Safety and Tolerability Assessments	Physical examinations, vital signs, 12-lead electrocardiograms, adverse events, hematology, serum chemistry, and urinalysis will be used to assess safety and tolerability.

PK Parameters	The PK profile of plasma pexidartinib will be analyzed by measurement of area under the plasma concentration-time curve [AUC_{0-t}, $AUC_{0-\infty}$], peak concentration (C_{max}), time to peak concentration (T_{max}), half-life ($T_{1/2}$), and terminal elimination rate constant (Kel). Dose proportionality following study medication will be explored by analyzing natural log-transformed pharmacokinetic variables, AUC_{0-t}, $AUC_{0-\infty}$, and C_{max}, with a linear model including the natural log-transformed dose as a covariate. Dose linearity for AUC_{0-t}, $AUC_{0-\infty}$, and C_{max} will also be explored by a linear model. PK assessments will be measured for each dose cohort of patients with correlations of C_{max} and AUC to any SAEs. Dose-response trends in C_{max} and AUC will be analyzed within each patient group for any suggestion of drug accumulation or alterations in PK based on concomitant medications.
PD Parameters	• Morning urine: N-Telopeptide of Type I Collagen (NTX) and C-Telopeptide of Type II Collagen (CTX-II) • Serum markers: Serum C-Telopeptide of Type I Collagen (CTX), Procollagen Type I Intact N-Terminal Propeptide (P1NP), Bone-specific Alkaline Phosphatase (BAP), Tartrate-Resistant Acid Phosphatase (TRAP 5b), Interleukin-6 (IL-6), Interleukin-1β (IL-1β), Matrix Metallopeptidase 3 (MMP-3), Erythrocyte Sedimentation Rate (ESR), C-Reactive Protein (CRP), Colony-Stimulating Factor-1 (CSF-1) • Blood markers: Circulating Tumor Cells (CTC), CD14+/CD16+ monocytes

TRIAL FLOW CHART (no Run-in Period)

STUDY DAY► / EVENT▼	Day –21 to -1	C1 D1[1]	C1 D2	C1 D8	C1 D15	C1 D16	C2 D1	D1 of C3+ [2]	End of Rx[3]
Informed Consent	X								
Medical History	X								
Height/Weight	X								
Physical Exam	X			X	X		X	X	X
Chem, Hem, Coag, UA	X			X	X		X [13]	X [13]	X
TSH	X						X	X	X
ECG [4]	X	X			X				
Vital Signs [5]	X	X		X	X		X	X	X
Plasma for PK [6]		X	X	X	X	X	X	X	
Pregnancy Test [7]	X								
ECOG Performance Status Assessment	X						X	X	X
Serum and Urine for Biomarker Assessment [8]		X		X			X		
Circulating Tumor Cell (CTC) Assessment [9]		X					X		
CD14+/CD16+ monocyte Assessment [10]		X		X					X
Radiographic Assessment of Tumor Burden [11]	X							X	
Test article compliance		X	X	X	X	X	X	X	X
Concomitant Medications	X	X	X	X	X	X	X	X	X
Adverse Events [12]		X	X	X	X	X	X	X	X

C = cycle; D = day; CxDx = Cycle x, Day x; UA = urinalysis

For footnotes, see Explanation of Subscripts below.

TRIAL FLOW CHART (with one-week Run-in Period)

STUDY DAY► / EVENT▼	Day -28 to -7	C1 D -7	C1 D -6	C1 D -4	C1 D1[1]	C1 D2	C1 D8	C1 D15	C1 D16	C2 D1	D1 of C3+[2]	End of Tx [3]
Informed Consent	X											
Medical History	X											
Height/Weight	X											
Physical Exam	X						X	X		X	X	X
Chem, Hem, Coag, UA	X						X	X		X [13]	X [13]	X
TSH	X									X	X	X
ECG [4]	X				X			X				
Vital Signs [5]	X	X			X		X	X		X	X	X
Plasma for PK [6]		X	X	X	X	X	X	X	X	X	X	
Pregnancy Test [7]	X											
ECOG Performance Status Assessment	X									X	X	X
Serum and Urine for Biomarker Assessment [8]					X		X			X		
Circulating Tumor Cell (CTC) Assessment [9]		X								X		
CD14+/CD16+ monocyte Assessment [10]		X	X	X	X		X					X
Radiographic Assessment of Tumor Burden [11]	X										X	
Test article compliance		X	X	X	X	X	X	X	X	X	X	X
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Events [12]		X	X	X	X	X	X	X	X	X	X	X

C = cycle; D = day; CxDx = Cycle x, Day x; Tx = treatment; UA = urinalysis

Explanation of Superscripts:

1 Day 1–16 apply to first cycle only.

2 If well tolerated and no tumor progression; clinic visits, laboratories at one month intervals with radiographic assessment performed every two months.

3 End or treatment or early withdrawal procedures should be completed within 30 days of the last dose of study drug and prior to initiation of any new therapy.

4 Triplicate ECG's (within 2 minutes apart) at screening and prior to dosing on C1D1, and at 2, 4, and 6 hours postdose on C1D1 and C1D15.

5 Blood pressure, respiratory rate, pulse, and oral temperature will be recorded predose and at each clinic visit noted; blood pressure and pulse will also be recorded 1 and 4 hours postdose on C1D1.

6 For QD dosing, obtained predose (AM) and 0.5, 1, 2, 4, and 8 hours postdose on C1D(-7), C1D1 and C1D15, and predose on C1D(-6), C1D(-4), C1D2 , C1D8, and C1D16. For BID dosing on C1D1 and C1D15, obtained predose (AM) and 1, 2, 4, and 7 hours postdose. The second dose will then be administered, and PK obtained 1 hour post the second dose (8 hours post the first dose). For BID dosing, no run-in is planned, with predose samples obtained on C1D2, C1D8, and C1D16. During continued dosing, obtained once every 4 weeks (predose). In the event of a DLT or SAE, a single blood sample should also be obtained within 48 hours.

7 For women of child-bearing potential; at screening should be within 7 days of first dose of study drug.

[8] Morning urine NTX and CTX-II and the following serum markers: CTX, P1NP, BAP, TRAP 5b, IL-6, IL-1β, MMP-3, ESR, CRP, CSF-1.

[9] Obtain blood sample for circulating tumor cells (CTC) predose (AM) on C1D1 and C2D1.

[10] Obtain blood sample for CD14+/CD16+ monocytes predose (AM) on C1D1 and C1D8; if feasible, also obtain a sample 1 week after discontinuing study drug.

[11] Screening window for radiographic assessment of tumor burden is 28 days.

[12] Monitored throughout the study via safety assessments, observation, and participant reporting.

[13] For all cycles after Cycle 1, a CBC with differential is required every 2 weeks (i.e., mid-cycle in addition to end of cycle).

TRIAL FLOW CHART – Extension Cohorts

STUDY DAY► / EVENT▼	Day –21 to -1 [1]	C1 D1	C1 D15 (±2 d)	C2 D1 (±7 d)	D1 of C3 to C40 [2] (±7 d)	D1 of C40, C43, C46, etc.+ [2] (±7 d)	End-of-Study/ Early Withdrawal[3]	12-Week Follow-up (LD + 12 wk +4 wk)[4]
Informed Consent	X							
Medical History	X							
Height	X							
Weight	X			X	X	X (unless remote)	X	
Physical Exam	X		X	X	X	X (unless remote)	X	
Chemistry, hematology, urinalysis	X		X[5]	X[5]	X[5]	X[5] (no urinalysis)	X	
ECG	X		X				X	
Vital Signs	X	X	X	X	X	X (unless remote)	X	
Plasma for PK [6]		X	X	X	X			
Pregnancy Test [7]	X						X	
ECOG Performance Status Assessment	X			X	X		X	
WOMAC Questionnaire [8]		X	X	X	X	X (unless remote)	X	
Numeric Rating Scale (NRS) for PVNS Symptoms Questionnaire to Patient [8]		X	X	X	X	X (unless remote)	X	
Dispense Numeric Rating Scale (NRS) for PVNS Symptoms Questionnaire for Outpatient Completion [9]	X		X	X	X	X (unless remote)		
Serum and Urine for Biomarker Assessment [10]		X		X				
Radiographic Assessment of Tumor Burden [11]	X				X	X (every 6 months)	X	X
Test Article Compliance		X	X	X	X	X (unless remote)	X	
Concomitant Medications	X	X	X	X	X	X	X	
Adverse Events [12]		X	X	X	X	X	X	
Collection of surgical data [13]							X	X

C = cycle; D = day; CxDx = Cycle x, Day x; LD = last dose; wk = week

[1] Screening window for radiographic assessment of tumor burden is 4 weeks.

[2] If well tolerated and no tumor progression; clinic visits, laboratories at 1-month intervals with radiographic assessment performed every two cycles. Radiographic assessment of tumor status can be performed every four cycles in patients who complete 14 cycles of treatment (i.e., reached Cycle 15 visit) and have Cycle 13 and Cycle 15 MRI scans that indicate SD or better per local RECIST v1.1 reading. For patients beyond Cycle 40, clinic visits will transition to every 12 weeks/3 cycles (remote serum chemistry and hematology as well as a telephone check-in for AEs and con meds and to review remote safety laboratory data may be performed in lieu of an on-site visit for subjects without ongoing Grade 2 or greater related adverse events; regular procedures not performed remotely include Weight, PE, Vitals, WOMAC, NRS, and IP compliance), with on-site visit and radiographic assessments performed every 24 weeks/6 cycles.

[3] End of Study or early withdrawal procedures should be completed 7-30 days after the last dose of study drug (or on the date of last dose of study drug for all subjects that enroll in the phase 4 continuation study) and prior to the initiation of any new anti-cancer therapy. If patient is starting commercially available drug then the end of study visit should be conducted before that transition.

[4] Visit only conducted for subjects that don't enroll in the phase 4 continuation study or transition immediately to commercial pexidartinib. For patients who miss the 30-day or 12-week post-treatment follow-up MRI, post-treatment radiographic assessments from any source (e.g., primary care provider) within 24 weeks of the last dose are acceptable.

[5] If there is a Grade 2 or higher ALT or AST elevation (i.e., >3 × ULN) at any time during treatment, the patient should be followed closely (see Section 14.7 for monitoring details).

[6] On C1D1, obtain predose. On C1D15, obtain predose (AM) and 1, 2, 4 and 6 hours postdose. During continued dosing, obtain once every 4 weeks (predose). For patients with afternoon clinic visits, see Section 20.1.

[7] For women of child-bearing potential.

[8] Patients enrolled after the implementation of Amendment 8 will complete these two patient reported outcome (PRO) instruments predose at the clinic on C1D1, C1D15, C2D1, and monthly thereafter, and every 12 weeks after C40, while continuing study drug administration, and at the End of Study visit.

[9] For patients enrolled after the implementation of Amendment 8, six (6) questionnaires will be dispensed at the indicated clinic visits with instructions and reminders to complete the questionnaire on an outpatient basis for 6 consecutive days (Day -6 to Day -1) prior to each monthly clinic visit on C1D1, C2D1, C3D1, etc. (or at every 12- or 24-week visit after C40) while continuing study drug administration. The patient should return the completed questionnaires to site staff at each of the subsequent monthly clinic visits on C1D1, C2D1, C3D1, etc.

[10] Morning urine NTX and CTX-II and the following serum markers: IL-6, CSF-1. CD14+/CD16+ monocytes predose (AM) on C1D1 only.

[11] This assessment will occur every 8 weeks during continued dosing, and every 24 weeks after C40, and (for subjects that don't enroll in the phase 4 continuation study or transition to commercial pexidartinib) approximately 30 days and 12 weeks after the last dose of study drug; additional detail regarding MRI is included in footnote 2. For PVNS patients, the Sponsor will receive radiologic images for possible retrospective analysis of treatment response, to be performed by a central vendor.

[12] Monitored throughout the study via safety assessments, observation, and participant reporting.

[13] If surgical resection of the tumor is performed within 12 weeks of the last dose of study treatment, details of the surgery and its outcome should be obtained. Tumor biopsy tissue may be submitted for biomarker analysis.

6.0 INTRODUCTION

6.1 Background

Kinases play a ubiquitous role in the signaling pathways for proliferation, metastasis, and survival of most tumor types. Pexidartinib is a potent and selective inhibitor of Fms (the receptor for macrophage-colony stimulating factor, M-CSF), Kit (the receptor for stem cell factor, SCF) and oncogenic Flt3 (the receptor for Flt3 ligand). Therefore, it has the potential to treat cancers through multiple mechanisms. For example, somatic activation of Kit and Flt3 has been well-documented in a number of cancers. Beyond the direct dependence of tumors on these oncogenic drivers, Fms and Kit are regulators of key components of the tumor microenvironment, namely macrophages, osteoclasts, and mast cells. Therefore, pexidartinib has effects on multiple aspects of tumorigenesis, including proliferation, intravasation, extravasation, and survival of metastases. The inhibition of these activities by pexidartinib has been characterized in cellular and in vivo assays. The pharmacologic efficacy demonstrated to date and the therapeutic promise support further development of pexidartinib as an anti-cancer therapeutic.

Pexidartinib is a novel, orally active, small molecule inhibitor that targets Fms, Kit and oncogenic Flt3, but remains highly selective versus other kinases. The potent inhibition of these three kinases can be exploited to attach tumors via different mechanisms: 1) directly inhibiting oncogenic drivers such as oncogenic Kit and Flt3 mutant proteins, 2) inhibiting paracrine loops between stromal cells and tumors, 3) blocking migration and angiogenesis, and 4) disrupting osteolytic metastases.

Tumor control due to blockade of Kit mutations has been validated in the clinic through the established efficacy of imatinib and sunitinib in gastrointestinal stromal tumors (Fletcher 2007). Clear tumor responses in patients with acute myelogenous leukemia (AML) using inhibitors of mutant Flt3 have also been reported, although none of these inhibitors has yet been approved to treat AML (Tam 2008). Pexidartinib may afford an advantage over other compounds in that very few ‘off-target’ kinases are inhibited. Indeed, pexidartinib preferentially inhibits oncogenic Flt3 versus the wildtype protein, providing promise for a wider therapeutic potential.

The efficacy of osteoclast antagonists such as bisphosphonates in preventing bone fractures and pain resulting from osteolytic metastases has been recognized for some time (Kohno 2008). Osteoclasts require the parallel activation of the RANK-L and Fms pathways for activity and survival. Recently, RANK-L antagonists have demonstrated efficacy to prevent bone destruction in preclinical models, and efforts to validate this in the clinic are well underway (Lipton 2008). As a potent inhibitor of Fms, the anti-osteoclast effects of pexidartinib that are seen in vitro and in vivo provide an alternative mechanism to block bone destruction and consequent pain.

More recently, an important role for tumor infiltrating macrophages in tumor progression has pointed to Fms as a key target in multiple tumor types (Coffelt 2009). The pro-tumorigenic role of CSF-1 and Fms is strongly supported by a wealth of studies demonstrating that CSF-1 levels predict a poor outcome in a variety of oncology indications, including breast, ovarian, non-small

cell lung, and colorectal cancers. Further strengthening the fundamental tumorigenic role of Fms is a key study showing that mice defective in CSF-1 are protected against tumor metastases.

Accordingly, treatment of breast cancer xenografts with anti-sense, antibodies or siRNA to CSF-1 suppresses tumor growth. The mechanism for this inhibition relates in part to a paracrine loop that links CSF-1 secreting tumor cells with EGF-secreting macrophages (Pollard 2008). Furthermore, a growing body of literature has now linked macrophages to angiogenesis (Coffelt 2009). One final aspect to tumorigenesis also implicates Fms, namely its role in the terminal differentiation of osteoclasts (Tanaka 2007). Coupled with the reported efficacy of bisphosphonates and RANK-L antagonists in tumor models, the anti-osteoclast activity of Fms inhibition should supplement the anti-macrophage mediated tumor suppressive potential. Taken together, this information provides a rationale for the role of Fms as a potentially important cancer target.

Finally, mast cells also comprise an important faction of the microenvironment of certain tumors. For example, in plexiform neurofibromas that cause significant morbidity in patients with neurofibromatosis type 1, a paracrine loop between mast cells and Schwann cells has been demonstrated in preclinical models (Yang 2008). Subsequently, pexidartinib has shown preliminary efficacy to reduce development of plexiform tumors in a mouse model of NF1.

6.2 Pharmacodynamics

In brief, biochemical data support Fms, Kit and oncogenic Flt3 as key targets of pexidartinib. Consequently, proliferation of cell lines that alternatively depend on M-CSF, SCF, or endogenous Flt3 that is oncogenically activated by internal tandem duplications (Flt3-ITD) is inhibited at IC_{50} values below 1 µM. Furthermore, M-CSF-induced autophosphorylation of Fms and SCF-induced autophosphorylation of Kit are potently inhibited by pexidartinib. By contrast, Flt3-ligand induced autophosphorylation of Flt3 and Flt3-ligand induced proliferation of cells are only weakly inhibited by pexidartinib, suggesting preferential inhibition of the oncogenically-activated kinase. Finally, the RANK-L and M-CSF-dependent differentiation of osteoclasts precursors is also potently inhibited by pexidartinib. These in vitro effects translated to effects in a variety of in vivo models designed to test the effects of pexidartinib on Fms-dependent proliferation, Fms-dependent osteoclasts differentiation, and Flt3-ITD dependent tumor growth.

6.2.1 In Vitro Pharmacodynamics

Pexidartinib shows significant selectivity versus a panel of over 200 kinases. Fms, Kit, and activated Flt3 appear to be the most sensitive target kinases, with IC_{50} vslues of 17, 12, and 9 nM, respectively (see Table 1).

Table 1: IC_{50} Values of Pexidartinib Against Selected Kinases

Kinase	Fms	Kit	Flt3	Kdr	Lck	Flt1	TrkC
Pexidartinib	17 nM	12 nM	9 nM	213 nM	860 nM	880 nM	890 nM

Kdr kinase activity is only modestly affected, and other kinases tested are even less sensitive to pexidartinib. While physiologic effects due to the inhibition of Fms and Kit are expected, the selectivity of pexidartinib suggests that minimal off-target effects should be observed. When screened against a broad panel of additional kinases, IC_{50} values were >1 μM for all, with the majority >10 μM.

Pexidartinib also demonstrated negligible activity in a standard Novascreen panel screen. This is a screen for off-target activity against a broad array of 71 targets in 8 families (Neurotransmitter-related, Steroids, Ion Channels, Nitric Oxide, Prostaglandins, Growth Factors, Brain/Gut Peptides, and Enzymes). At a concentration of 10 μM serum-free, all results were within 40% of Baseline, indicating no relevant off-target activity.

M-NFS-60 cells and BAC1.2F5 cells are mouse cell lines that require M-CSF to proliferate, and Mo7E cells are human cells that require SCF to proliferate. The ligand dependent proliferation of these cells is inhibited by pexidartinib with IC_{50}s of 0.33, 0.23 and 0.31 μM, respectively. In THP-1 cells, Fms autophosphorylation induced by M-CSF can be inhibited by 7 nM concentrations of pexidartinib. In Flt3-ITD-expressing MV4-11 cells, ligand-independent autophosphorylation of Flt3 is potently inhibited by pexidartinib with an IC_{50} of 26 nM. By contrast, in RS4:11 cells, Flt3 autophosphorylation can be induced by Flt3 ligand and this autophosphorylation requires high levels of pexidartinib (1500 nM) for inhibition. This weak inhibition of Flt3-ligand effects suggests that pexidartinib binds only weakly to unactivated Flt3. Finally, human osteoclast precursor cells can be induced to differentiate in to mature osteoclasts by the combination of RANK-L and M-CSF. Pexidartinib inhibits this osteoclast differentiation with an IC_{50} of 33 nM.

6.2.2 In Vivo Pharmacodynamics

Models of Fms-dependent proliferation and Fms-dependent osteoclast activity can be inhibited by 5–10 mg/kg doses of pexidartinib in vivo. This was demonstrated in a Fms-dependent splenomegaly model, a metastatic breast cancer model, and a murine collagen-induced arthritis model.

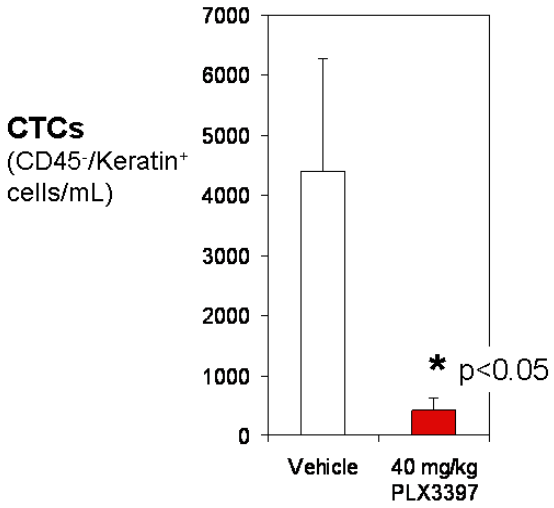
BaF3 cells are mouse pre-B cells that depend on interleukin-3 (IL-3) for survival. By engineering BaF3 cells to express BCR-activated Fms kinase activity, the dependence on IL-3 can be replaced. Consequently, these BCR-Fms expressing BaF3 cells are dependent on Fms kinase activity for survival. In vitro, proliferation of these cells can be potently inhibited by pexidartinib, with an IC_{50} of 7 nM. A corresponding BaF3 cell line expressing BCR-Kit is also quite sensitive to pexidartinib, with an IC_{50} of 130 nM.

Injection of the BCR-Fms-expressing BaF3 cells into the tail vein of nude mice results in homing of these cells to the spleen and subsequent cellular proliferation that results in dramatic

splenomegaly over the course of 14–18 days. Oral dosing of pexidartinib for the final 8 days of this model results in dose-dependent inhibition of the splenomegaly. The ED_{50} of this effect is between 2 and 5 mg/kg. Therefore, we believe that a 5 mg/kg oral dose of pexidartinib in mice corresponds to an efficacious dose. Pharmacokinetic analysis reveals that this 5 mg/kg dose achieves an $AUC_{0–24}$ of 99.8 µM•h, and a C_{max} of 13.4 µM. We will use these values to define an efficacious exposure, and this will be used the denominator in calculations of therapeutic multiples.

In a separate model, mice expressing the polyoma middle T antigen (PyMT) behind a mammary promoter develop breast cancer that metastasizes after several months. During the metastatic process, circulating tumor cells that express PyMT can be measured among circulating blood cells. Since Fms activity is a critical component of extravasation into the blood stream, reduction in the number of these circulating tumor cells can be a measure of anti-Fms activity. Within 24 hours of a single oral dose of 40 mg/kg pexidartinib, a 10-fold decrease in these circulating tumor cells can be determined (see Figure 1).

Figure 1: Pexidartinib-Induced Reduction of Circulating Tumor Cells in PyMT Mouse Model of Breast Cancer

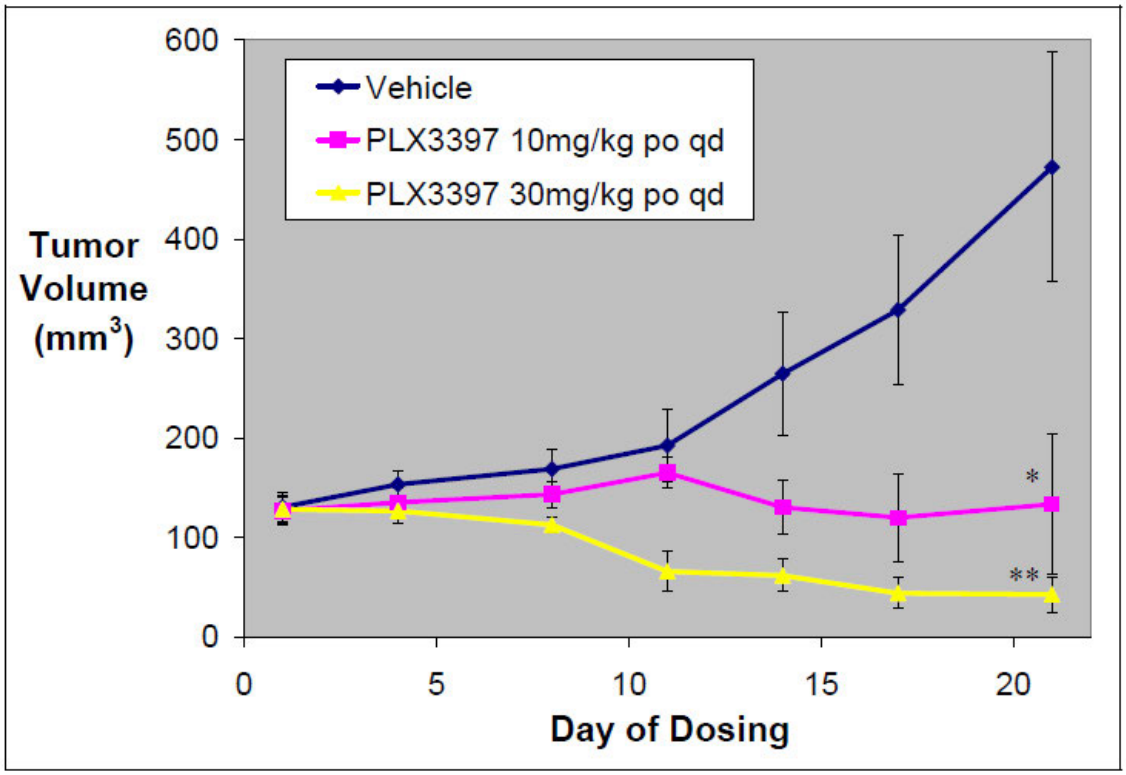


In order to determine effects of pexidartinib on osteoclastic activity in vivo, a murine collagen-induced arthritis model was implemented. In this model, double immunization of the mice with collagen leads to progressive clinical symptoms resembling rheumatoid arthritis. Histology can be used to measure osteoclasts that contribute bone-destructive pathology in this model. Osteoclasts are measured using an osteoclast-specific marker, namely tartrate-resistant acid phosphatase 5B (TRAP 5B). Treatment of these mice with 50 mg/kg pexidartinib over the course of 24 days results in significant stabilization of disease, and this is accompanied by dramatic reductions in macrophages infiltrating the joints. Importantly, joint-infiltrating osteoclasts are also reduced by 10-fold, illustrating the potent anti-osteoclastic effects of pexidartinib.

Since pexidartinib permeates the blood-brain barrier and Fms-dependent microglia are likely mediators of pain transmission, pexidartinib was tested in a formalin-pain model. This formalin model measures both acute nociceptive and acute inflammatory pain responses. Pexidartinib showed reduction in both phases of the formalin pain response, suggesting that effects on both acute and inflammatory pain may be expected in further studies.

As pexidartinib is a potent inhibitor of the proliferation of Flt3-ITD-dependent MV4-11 cells (cells derived from a patient with acute myelogenous leukemia) in vitro, the effect of pexidartinib treatment in an MV4-11 xenograft model was investigated. MV4-11 cells were implanted subcutaneously in the flank of male nude mice using matrigel as an adsorbing matrix. Once these tumors had been established to a size of >100 mm^2, treatment with 10 and 30 mg/kg/day oral doses of pexidartinib was initiated and continued for 3 weeks. This pexidartinib treatment was quite efficacious, resulting in tumor stabilization and some tumor regression at the 10 mg/kg dose and considerable tumor regression at the 30 mg/kg dose (see Figure 2). Indeed, half of the mice treated with 30 mg/kg pexidartinib had no palpable tumor at the end of 3 weeks of treatment. These data provide considerable rationale for testing for clinical efficacy of pexidartinib in acute myelogenous leukemia patients whose tumor cells bear Flt3-ITD mutations.

Figure 2: **Daily Oral Dosing of Pexidartinib Results in Dose-Dependent Tumor Suppression in MV4-11 Xenograft Model of Flt3-ITD Dependent Acute Myelogenous Leukemia**



* p<0.05, ** p <0.005

Please refer to the Investigator's Brochure for updated information and detailed description of the nonclinical pharmacology data.

6.3 Nonclinical Metabolism and Pharmacokinetics

Please refer to the Investigator's Brochure for updated information and detailed description of the nonclinical metabolism and PK.

Pexidartinib has low aqueous solubility and modest permeability. It is not a substrate or inhibitor of Pgp. Several studies in four species (mouse, rat, dog and monkey) evaluated formulations to optimize absorption and systemic exposure following oral administration. Pexidartinib was absorbed within two to three hours following oral administration. In several studies, plasma exposure (based on AUC values) was greater in females (up to 34% in rats). Elimination half-lives ranged from 2 to 5 hours in these four species. A study conducted in cynomolgus monkeys showed that food does not inhibit or delay absorption of pexidartinib following oral (gavage) administration.

The extent to which pexidartinib binds to the plasma proteins was evaluated in vitro using a Rapid Equilibrium Dialysis inverted method. Pexidartinib is strongly protein bound in plasma for all four species tested (mouse, rat, dog, and human). With regards to potential species differences, the binding in mouse, dog and human plasma at 75 µM was approximately equal (99.8%, 99.7%, and 99.8% respectively) while rat protein binding was marginally lower (98.3%).

Two experiments evaluated the partitioning of pexidartinib between blood and brain, based on measurements of test article in brain tissue, cerebrospinal fluid and plasma. In one study, appreciable amounts of pexidartinib were recovered in whole blood (vs. plasma), suggesting that pexidartinib associates with cellular elements of blood. In experiments that quantified pexidartinib concentration in brain tissue and cerebrospinal fluid 4 and 6 hours following oral administration in rats, the brain:plasma ratio averaged 0.41 and 0.36, respectively - values close to that of antipyrene, a positive control (0.50 and 0.54). The ratios of CSF:plasma at these timepoints for pexidartinib, however, were lower (0.026 and 0.014) than those for antipyrene (1.06 and 0.92).

A series of in vitro studies examined the metabolic stability of pexidartinib using either liver S9 fraction or intact hepatocytes from several species, including rats and dogs, the two species used in toxicology studies, as well as humans. Studies with intact hepatocytes revealed that pexidartinib was very slowly metabolized in all three species, especially human liver cells. Although the exact molecular species were not identified, in the presence of human hepatocytes, several molecular species corresponding to glucuronide conjugates were detected, with minimal evidence of breakdown. These data, along with the high protein binding, suggests that the clearance of pexidartinib from human plasma may be slow. Another study was conducted to

evaluate the CYP450 phenotypes of pexidartinib metabolism in vitro. Of the five major CYP isoforms, 3A4 (BFC) may be involved in Phase I metabolism of pexidartinib, with possibly CYP1A2 playing a minor role.

Pexidartinib does not appear to inhibit CYP drug-metabolizing enzymes to an important extent. Studies using human liver microsomes yielded enzyme inhibitory constant (K_i) values exceeding 30 µM for CYP1A2 and 3A4 (testosterone substrate), ≥12 µM for 3A4 (midazolam substrate), 2D6 and 2C9. A K_i value <10 µM was obtained for only one CYP isozyme: 2C19 (K_i = 8.4 µM). It is worth noting that the latter experiment was conducted in the absence of HSA. When pexidartinib was evaluated for its ability to inhibit the major human CYP isozymes in the presence of 10 µM human serum albumin (HSA), IC_{50} values greater than 30 µM were uniformly obtained.

In another series of experiments, pexidartinib was demonstrated not to induce the expression of genes that encode CYP enzymes and several other proteins involved in metabolism and transport.

In aggregate, an extensive series of non-clinical studies evaluating pexidartinib reveal a metabolically stable drug that displays extensive protein binding. Clinically relevant drug-drug interactions are not anticipated based upon experimental evidence of negligible CYP inhibition or induction in vitro.

6.4 Summary of Nonclinical Toxicology and Safety Pharmacology

After establishing dose-response systemic exposure data with gavage formulations of pexidartinib, the toxicology was evaluated in non-GLP repeat dose and GLP 28-day repeat-dose toxicity studies in Sprague-Dawley rats and Beagle dogs. Standard GLP batteries of genotoxicity and safety pharmacology studies were also performed.

Results of the studies are presented below. In summary, a NOAEL for either species was not determined, based on body weight losses and several histological and/or gross morphological effects. However, the significant test article-related adverse effects (testes, ovaries, bone and bone marrow, hematology and lymphoid changes) are consistent with the pharmacological mechanism of action of pexidartinib. Importantly, all of these findings were partially or fully reversible. There were no safety findings in the genotoxicity and safety pharmacology studies.

Please refer to the Investigator's Brochure for a more detailed description of the non-clinical toxicology and safety pharmacology studies.

6.4.1 Repeat-Dose Toxicity in Rats

In rats administered pexidartinib by oral gavage for 7 days at doses of 30, 100, and 300 mg/kg/day, there were modest potential test article-related effects as follows: decreased WBC and hemoglobin, increased AST, ALT, alkaline phosphatase, increased liver and decreased

spleen weights, bone marrow hematopoietic atrophy, and cystic corpora lutea. Under the conditions of this study the NOAEL was 30 mg/kg/day for males and females.

In the subsequent GLP 28-day study with a 14-day recovery period, Sprague-Dawley rats were dosed at 20, 60, and 200 mg/kg/day. Exposure increased as dosage was increased over the 20 to 200 mg/kg/day range for both sexes, with exposure in females tending to be modestly higher (9-34%, depending on dose) compared to males.

Non-adverse lower body weights and food consumption were noted for the 200 mg/kg/day group females. Body and food consumption effects resolved during the recovery period.

Changes in hematology parameters consisted of dose-related lower WBC, RBC, PT, aPTT, and lower reticulocyte counts in all test article-treated groups. At study day 43 recovery evaluation, the WBC counts had rebounded, the RBC mass partially recovered, reticulocyte counts were higher than the control group, and fibrinogen, PT, and APTT had resolved in the 200 mg/kg/day groups. Alterations in hematology are likely related to the mechanism of pexidartinib-mediated inhibition of Fms and Kit kinase. No effects on clinical chemistry were considered adverse.

There were macroscopic findings of discoloration/red areas of the ovaries in the 60 and 200 mg/kg/day females at primary necropsy, and soft/small testes in the 200 mg/kg/day group males at the recovery necropsy. Microscopic alterations included dose-related minimal to moderate subphyseal hyperostosis in the femur for the 60 and 200 mg/kg/day groups, minimal to moderate physeal hypertrophy in the femur for the 60 and 200 mg/kg/day groups, and dose-related reduction in the density of hematopoietic cells of all lineages within the bone marrow (sternum and femur). Alterations in bone parameters are likely related to the mechanism of pexidartinib-mediated inhibition of Fms and Kit kinase. Dose-related hepatocellular centrilobular hypertrophy was noted for the 200 mg/kg/day groups and correlated with higher liver enzyme levels and higher liver weights, and a higher incidence and/or severity of chronic progressive nephropathy was noted for the 200 mg/kg/day groups. This finding is a normal spontaneous change in Sprague-Dawley rats and was noted in the vehicle control groups. Microscopic findings in the skin and lymphoid tissues included a dose-related higher incidence of minimal to mild myxomatous change in the skin/subcutis of all test article-treated groups, and lymphoid depletion of the cortex in the thymus in the 60 and 200 mg/kg/day groups.

Microscopic findings in endocrine and reproductive tissues included dose-related higher incidence and severity of hemorrhagic corpora luteal cysts in the ovaries in the 60 and 200 mg/kg/day females, dose-related higher incidence and/or severity of thyroid follicular cell hypertrophy in the 200 mg/kg/day groups. Minimal to moderate depletion of spermatogenic epithelium at study day 28/29 was noted in the 60 and 200 mg/kg/day group males, and the 200 mg/kg/day group males were often completely devoid of spermatogonia and pachytene spermatocytes. Tubules in stages of elongation were frequently characterized by complete absence of prepachytene and pachytene spermatocytes and sertoli cell vacuolization was occasionally observed. At study day 43, the 200 mg/kg/day group males had depletion of

spermatogonic epithelium and mild to severe atrophy characterized by a depletion of spermatids, however there was an increase in the spermatogonial population, which is reflected by the presence of significant numbers of early prepachytene (leptotene and zygotene) spermatocytes. Alterations in testes and ovaries are likely related to the mechanism of pexidartinib-mediated inhibition of Fms and Kit kinase.

The majority of alterations in morphologic pathology parameters, except for luteal cysts and chronic progressive nephropathy, partially or completely resolved following the recovery period. Luteal cysts reduced in severity but remained higher than the control group in the 200 mg/kg/day group females. On the basis of observations made in this GLP-compliant study, a no-observed adverse effect level (NOAEL) for oral (gavage) administration of pexidartinib was not determined. This study also did not establish a lethal dose in 50% of rats LD_{50} or severely toxic dose in 10% or rats (STD10). However, for the purposes of calculating a clinical starting dose for oncology, Plexxikon has assumed the highest dose tested in this study (200 mg/kg) to be the STD10.

6.4.2 Repeat-Dose Toxicity in Dogs

In two pairs of Beagle dogs administered pexidartinib at a dose of 600 mg/kg BID (1200 mg/kg/day) for 7 days, findings included emesis and mild to moderate reduction of erythropoiesis in bone marrow. Mild body weight loss was likely secondary to emesis.

In the subsequent GLP toxicity study, groups of Beagle dogs were administered pexidartinib for 28 days at doses of 100, 300, and 1000 mg/kg/day which was then reduced to 50, 100, and 300 mg/kg/day after the first week due to lethargy, weight loss, and lack of food consumption in several high dose animals.

Mean exposure generally increased as dosage increased over the 50 to 1000 mg/kg/day range, but the range of exposure observed for individual animals within a dose group frequently overlapped between the dosages of 50 and 100 mg/kg/day and 300 and 1000 mg/kg/day doses. Exposure tended to be similar in males compared to females.

There were no test-article-related ophthalmic or macroscopic findings or effects on urinalysis, ECG or organ weight parameters.

Three dogs in the 1000/300 mg/kg/day group were euthanized in extremis on study days 8, 15, and 17 due to prostration, tremors, impaired coordination, and tachypnea. Emesis was noted in all groups with an increased incidence in the 300/100 and 1000/300 mg/kg/day groups.

Modest body weight declines were observed for the 300/100 and 1000/300 mg/kg/day group; primarily from study week 0 to 1. These changes correlated with decreased food consumption and were reversible during the recovery period.

Changes in hematology parameters consisted of time- and dose-related declines in RBC mass and reticulocyte counts at 1000/300 and 300/100 mg/kg/day, which correlated with bone marrow hypocellularity resulting in a non-regenerative anemia at study week 2. The anemia increased in severity at study week 4, despite a rebound in absolute numbers of reticulocytes. These effects were considered adverse though reversible, based on partial recovery noted at study week 6. Higher fibrinogen levels were also noted in all dose groups. Alterations in hematology are likely related to the mechanism of pexidartinib-mediated inhibition of Fms and Kit kinase.

There were no adverse test article related serum chemistry effects. Hypophosphatemia was noted in males at dosage levels >300/100 mg/kg/day and in females at doses >100/50 mg/kg/day. Elevated levels of PTH in the 300/100 and 1000/300 mg/kg/day groups may have contributed to the hypophosphatemia but was reversible and not severe enough to be considered adverse. Additionally, Fms inhibition can reduce osetoclast differentiation and function, resulting in decreased bone resorption and decreased serum phosphate.

Pexidartinib caused significant, partially reversible testicular atrophy at all three doses. The earliest changes, noted in two 1000/300 mg/kg/day group males euthanized in extremis, were severe, with diffuse spermatocytes and spermatid degeneration. At study week 4, the atrophic tubules contained small numbers of retained spermatids and degenerate/multinucleate intra-luminal spermatids.

Pexidartinib-related alterations were less prominent in the ovary, possibly because most ovaries were immature. Follicular degeneration, characterized by large, distorted, antral follicles with extensive apoptosis of granulose cells and a peripheral stromal cell proliferation, was noted in two of three females administered 1000/300 mg/kg/day. There appeared to be an increased number of atretic follicles in one of two affected dogs. Alterations in testes and ovaries are likely related to the mechanism of pexidartinib-mediated inhibition of Fms and Kit kinase.

Bone marrow exhibited a dose-related minimal to mild hypocellularity. Following a 14-day recovery, the bone marrow from the 1000/300 mg/kg/day group was minimally hypercellular, demonstrating recovery. In the spleens, minimal to mild increased extramedullary hematopoiesis was noted in all dose groups. The extramedullary hematopoiesis was an expected physiologic response to the decreased RBC mass and regenerative anemia.

In the femur, minimal to moderate subphyseal hyperostosis was evident in dogs that received 300/100 and 1000/300 mg/kg/day. Hyperostosis was not evident at study week 6. This lesion was characterized by a retention and elongation of the primary spongiosa beneath the physis and was considered a reversible consequence of pharmacologic effect on osteoclasts.

Lymphoid depletion was evident in the thymus, lymph nodes, Peyer's patches, and spleen more frequently, compared to vehicle controls. These effects were considered to be secondary to Pexidartinib-related nonspecific stress factors; however, an organ-specific test article-related effect on the lymphoid system cannot be excluded.

Minimal to mild valvular endocardiosis was occasionally noted in placebo- and pexidartinib-treated dogs at study weeks 4 and 6. Because this finding can occur spontaneously and a clear dose-response was not observed, it was likely not a direct pexidartinib-related effect. Additionally, minimal subendothelial myxomatous change was noted in four dogs treated with pexidartinib at the primary necropsy. This alteration was characterized by focal increases in proteoglycans near the luminal surface of the aorta. While regional variation in proteoglycan content was considered within normal limits and the change could have been part of the normal spectrum, a pexidartinib-related effect cannot be ruled out. Importantly, no evidence of myxomatous change in the aorta was noted in the 28-day rat GLP toxicology study where high-dose unbound pexidartinib exposure was 18-fold that seen at the high-dose in the dog study.

In the kidneys, basophilic tubules were noted in the 100/50 (females only) 300/100 and 1000/300 mg/kg/day groups with no clear relationship to the pexidartinib dose administered. Basophilic tubules are a common spontaneous finding in control group dogs. The incidence of findings was within the range of those noted in the database of historical control groups. Thus the kidney findings were considered of uncertain relationship to the test article.

Based on the results of this study, systemic toxicity of pexidartinib administered orally by gavage twice daily for 28 consecutive days was observed at dosage levels of 300/100 and 1000/300 mg/kg/day, as evidenced by mortality (1000/300 mg/kg/day), adverse clinical observations of emesis, and emesis-related findings, body weight losses with associated low food consumption, and microscopic findings of the testes, bone marrow, kidneys, spleen, and lymphoid depletion in the thymus. Therefore, a NOAEL was not determined. This study also did not establish a lethal dose in 50% of dogs LD_{50}. For the purposes of calculating a clinical starting dose for oncology Plexxikon has defined the 300 mg/kg dose to be the highest nonseverely toxic dose (HNSTD) in dogs.

6.4.3 Genotoxicity

No signs of genotoxicity were identified in a standard battery of tests (in vitro AMES and chromosomal aberration and in vivo micronucleus assays) conducted with pexidartinib.

6.4.4 Safety Pharmacology

In GLP-compliant respiratory and central nervous system safety studies, the NOEL for pexidartinib was 200 mg/kg in rats. Additionally, three GLP-compliant safety pharmacology studies addressed the potential adverse cardiovascular or cardiac electrophysiological effects of pexidartinib. When evaluated in a serum free hERG study, pexidartinib was shown to bind to the channel (IC_{50} 0.7 μM). However, in a follow-up cardiac Purkinje fiber study, no test article-related effects on repolarization, AP amplitude or speed of cardiac depolarization were observed. Furthermore, in a dog in vivo GLP cardiovascular safety study, all electrocardiographic parameters were qualitatively and quantitatively within normal limits, demonstrating that pexidartinib does not prolong cardiac repolarization up to the highest dose tested (1000 mg/kg).

7.0 RATIONALE

This study will provide an assessment of the safety, tolerability, PK, and PD activity of ascending doses of pexidartinib in patients with solid tumors. Each of six Extension cohorts will evaluate the potential of pexidartinib to provide clinical responses in these disease settings. These diseases consist of the following: mucoepidermoid carcinoma (MEC) of the salivary gland, pigmented villo-nodular synovitis (PVNS), gastrointestinal stromal tumor (GIST), anaplastic thyroid carcinoma (ATC), solid tumors with malignant effusions, and a cohort of miscellaneous tumors. The rationale for initiation of these Extension cohorts is based on clinical responses observed in the dose escalation phase of the study as well as available literature support and specific pharmacology data with pexidartinib. A favorable benefit-risk ratio in an Extension cohort is likely to result in additional clinical development of pexidartinib in that indication.

For MEC of the salivary gland, tumor-associated macrophages (TAMs) are strongly associated with tumor grade and stage (Shieh 2009), high levels of CSF-1 are expressed in saliva, and a dose escalation patient with MEC of the salivary gland had a pronounced and confirmed PR during treatment with pexidartinib. For PVNS, CSF-1 translocations can result in overexpression of CSF-1; the majority of cells express Fms, suggesting a tumor-landscaping effect with aberrant CSF1 expression in the neoplastic cells, leading to the abnormal accumulation of non-neoplastic cells that form a tumorous mass (West 2006). For GIST, pexidartinib has potent activity on both wild type Kit as well as acquired Kit mutations in exon 13 that are resistant to both imatinib and sunitinib (Liegl 2008). For ATC, recent work has highlighted the role of TAMs in the progression of thyroid cancers, and ATC in particular harbors abundant TAM infiltration (Ryder 2008). In-house data support that pexidartinib significantly reduces TAM levels. Malignant effusions are associated with high levels of M2 inflammatory macrophages, CSF-1, and inflammatory mediators such as IL-6 (Kaczmarek 2011). Additionally, the dose escalation patient with MEC of the salivary gland had a profound decrease in her pleural effusions.

7.1 Dose Escalation

The selection of the starting dose of 200 mg QD is based on in vivo data from nonclinical pharmacological models, toxicologic results, and estimated PK parameters for humans.

In accordance with guidelines for starting dose selection for investigational agents in cancer patients, dose ratios were calculated using the severely toxic dose in 10% (STD10) in rats and non-rodent highest non-severely toxic dose (HNSTD). The rat 28-day repeated-dose toxicology study did not establish a lethal dose in 50% of animals (LD_{50}) or a STD10. However for the purposes of calculating a clinical starting dose for oncology, Plexxikon has assumed the highest dose tested in the rat study (200 mg/kg) to be the STD10. The dog study also did not establish a LD_{50}, and thus the 300 mg/kg dose was considered to be the HNSTD. Using this algorithm and estimating the rat 1/10 x STD10 to be 20 mg/kg, a maximum recommended starting dose (MRSD) of 200 mg (or ~120 mg/m2) is proposed. Based on a comparison the 1/10 x STD10

(after converting mg/kg dose to mg/m2) to either the efficacious dose in the mouse BaF3 model or the proposed human MRSD of 200 mg, dose ratios for the rat (vs. human) were 13 and 1, respectively. The dose ratios in the dog, based on these assumptions and estimating the dog 1/6 x HNSTD to be 50 mg/kg, were 111 and 8.

Safety margins were also calculated by comparing values for free drug exposure (AUC) in rats and dogs at their 1/10 STD or 1/6 HNSTD, respectively. Pexidartinib is strongly protein bound in plasma of dogs, rats, and humans thus the fraction of pexidartinib unbound is a more meaningful comparison. In the comparison of rat *vs*. human, this method yielded an exposure ratio of 72, based on the predicted AUC of 14 ng•hr/mL at the proposed MRSD of 200 mg. Applying the same method of comparison and assumptions, exposure ratios of 2.4 and 10 were obtained for dog *vs.* human.

In the case of calculating safety margins based on free drug exposure, the safety margin based upon the maximum recommended starting dose in humans is 10 or above. Thus, based on either dose ratios or free drug exposure ratios, the proposed MRSD of 200 mg in humans should represent a minimally effective dose with only a limited safety risk.

For dose escalation planning, the effects of pexidartinib on bone marrow appear to be the most predictive of Fms and Kit activity on normal tissue. In both rats and dogs, both the incidence and severity of bone marrow hypocellularity with resulting decreased peripheral WBC counts is approximately linear with increasing dose and systemic exposure. This supports the planned dose escalation design as proposed in Section 16.4.

7.2 Route and Regimen

Oral dosing with pexidartinib is planned for this study. Adequate systemic exposure is expected by oral administration. The proposed regimen for the first cohort is once daily. A twice-daily dosing regimen may be instituted for subsequent cohorts after review of the PK data from the initial cohort. For the Extension cohorts, the dose regimen is BID.

7.3 Treatment Period

The proposed treatment period of 28 days (initial phase) was initially supported by 28 days of GLP general toxicology studies in 2 species for the 200 mg starting dose. Pexidartinib will be offered to each patient as long as both the patient and investigator agree that it continues to be well tolerated, and there has been no evidence of clinical disease progression.

8.0 OBJECTIVES

8.1 Primary

The primary objective for the dose escalation phase of this study is to evaluate the safety and PK of pexidartinib in patients with solid tumors. The primary objective of the Extension cohorts is to evaluate the potential of pexidartinib as a single agent to provide clinical benefit in patients with

specific malignancies, based on literature, pharmacology data, or responses in the dose escalation phase of the study.

8.2 Secondary

The secondary objective is to measure the pharmacodynamic activity of pexidartinib via plasma and urine biomarkers of Fms activity (all cohorts).

9.0 DESIGN

9.1 Description

Dose Escalation Cohorts:

This is an open-label, ascending dose trial of daily oral doses of pexidartinib administered to patients with solid tumors at approximately 4 investigational sites. A cohort of 3 patients will be assigned to the first dose group to receive 200 mg QD of pexidartinib. PK samples will be obtained after the first dose (through 8 hours) on C1D1 and prior to the first dose on C1D2. Patients will return to the clinical site on C1D8 for assessment of adverse events, PK (predose), and clinical laboratory assessments. They will then return to the clinic on C1D15 for evaluation of safety (AEs, clinical laboratory assessments, vital signs, ECG) and PK. Each cycle is defined as 28 days. If adequate safety and tolerability have been demonstrated for one cycle of 28 days at this dose level, the next cohort of 3 patients will be enrolled and treated with pexidartinib once or twice daily in a similar fashion as the first cohort. Each cohort will return to the clinic after 4 weeks of dosing for a repeat evaluation of safety. Three patients will be enrolled to each dose level in the absence of Grade 2 or greater drug-attributable toxicity. Dose escalations of 100% are planned until the occurrence of drug-attributable Grade 2 or greater toxicity. In the absence of DLT, dose escalation will proceed sequentially by 50% increments from that point forward.

In selected cohorts, 3–6 patients will be treated with a pexidartinib dose of either 100 mg QD or 200 mg QD during a one-week run-in period before increasing to the full dose for that cohort, in order to profile the pharmacodynamic (PD) dose response activity of pexidartinib at doses below 300 mg QD.

Assignment of patient study numbers and verification of dose selection will be coordinated by the CRO assigned by the Sponsor, in collaboration with the Sponsor. A teleconference attended by the participating investigators, the CRO personnel, and the Sponsor will be held weekly or as needed to assess cumulative safety data and jointly confirm a decision to expand a cohort or dose escalate, in accordance with the criteria set forth in Section 16.4.

After the initial 4 weeks of dosing, all patients will be able to continue receiving pexidartinib at their assigned dose provided they meet the criteria described in Section 13.8. Patients will return for clinical evaluation every 28 days and will have radiographic assessments (solid tumors) for response and progression after every two months of drug administration.

Extension Cohorts:

At the recommended Phase 2 dose of 1000 mg/day, a total of six Extension cohorts will be enrolled and followed for safety and tumor response as assessed by CT scan every 8 weeks (or, beyond Cycle 40, every 24 weeks). Participants will remain on treatment until tumor progression, as long as there are no unacceptable toxicities.

9.2 Number of Patients

Up to 50 patients will participate in the study in the dose escalation phase of the study. Approximately 10 patients will be enrolled in each of the five disease-specific Extension cohorts and up to 20 patients can be enrolled in the miscellaneous Extension cohort, for a total of approximately 70 patients with the possibility of 30 additional patients in a specific cohort if necessary (Section 24.6).

9.3 Number of Study Centers

For dose escalation, the study will be performed at approximately 4 investigational sites. For the extension cohorts, up to approximately 18 sites will participate.

9.4 Duration of Patient Participation

Each patient in the dose escalation phase of the study will participate in the study for 4 weeks at the designated dose, and then will be offered continued dosing with pexidartinib if it is well tolerated and in the absence of tumor progression. Patients in the Extension cohorts will be offered continued dosing with pexidartinib if it is well tolerated and in the absence of tumor progression.

9.5 Duration of Study

The duration of the study is contingent on the number of dose levels in the dose escalation phase. Each dose escalation cohort will take approximately 6 weeks (7 weeks for cohorts that include a one-week run-in period), including 2 weeks of recruitment. For the Extension cohorts, patients will be treated with study drug until progression or toxicity, until the phase 4 PVNS continuation study has been opened. Upon study termination, patients that don't transition to the phase 4 continuation study will be provided information regarding potential transition to commercial drug.

10.0 SELECTION OF STUDY POPULATION

All patients must participate in the consent process. During the consent process, the person obtaining consent must inform the patient of all elements of informed consent. No protocol-specific procedures, including screening procedures, are to be performed until the patient has signed and dated an institutional review board (IRB)/independent ethics committee (IEC)-

approved informed consent form. The study begins with the signing and dating of the informed consent form. Patients must also meet the inclusion and exclusion criteria to be enrolled in the study.

10.1 Inclusion Criteria

1. Male or female patients ≥18 years old
2. For the dose escalation cohorts, patients with advanced, incurable, solid malignancies in which the target kinases are thought to be linked to disease pathophysiology and whose cancers are confirmed histologically. The tumors must fulfill BOTH of the following criteria: a) refractory to standard therapy, OR standard or curative therapy does not exist or is not considered appropriate by the investigator, AND b) tumor proliferation or metastasis could be driven or promoted in part by Flt3, Kit, or Fms/CSF-1 activity.
3. For the Extension cohorts, patients must have measurable disease by RECIST v1.1 criteria and meet the following disease-specific criteria:
    a. For advanced or recurrent MEC of the salivary gland, patients must not be candidates for curative surgery or radiotherapy.
    b. For PVNS (including tenosynovial giant cell tumor), patients must have a histologically confirmed diagnosis of inoperable progressive or relapsing PVNS, or resectable tumor requiring mutilating surgery, as well as demonstrated progressive disease in the last 12 months.
    c. For GIST, patients must have failed previous therapy with imatinib and sunitinib. Patients with known PDGFR mutations are excluded, but mutation testing is not required for study entry.
    d. For ATC, patients must have histologically or cytologically diagnosed advanced ATC.
    e. For metastatic solid tumors with documented malignant pleural, pericardial, and/or peritoneal effusions, patients must not be receiving specific therapy for the effusion (other than periodic drainage by needle) or have an indwelling drain.
    f. Other solid tumor types can be included in a miscellaneous cohort, provided there is a clear scientific rationale for treatment with pexidartinib and upon approval by the Medical Monitor.
4. Women of child-bearing potential must have a negative pregnancy test within 7 days of initiation of dosing and must agree to use an acceptable non-hormonal method of birth control from the time of the negative pregnancy test up to one month after the last dose of study drug, Women of non-childbearing potential may be included if they are either surgically sterile or have been postmenopausal for ≥1 year. Fertile men must also agree to use an acceptable method of birth control while on study drug and for one month after the last dose of study drug.
5. All associated toxicity from previous or concurrent cancer therapy must be resolved (to ≤Grade 1 or Baseline) prior to administration of pexidartinib.

6. Willing and able to provide written informed consent prior to any study related procedures and to comply with all study requirements.
7. ECOG performance status 0 or 1.
8. Life expectancy ≥3 months.
9. Adequate hematologic, hepatic, and renal function (absolute neutrophil count ≥1.5 x 10^9/L, Hgb >9 g/dL, platelet count ≥100 x 10^9/L, AST/ALT ≤2.5 x ULN or <5 x ULN in the presence of liver metastases, albumin ≥3 g/dL, creatinine ≤1.5 x ULN or calculated CrCl >60 mL/min using Cockcroft-Gault formula).

10.2 Exclusion Criteria

1. Specific anti-cancer therapy within 3 weeks prior to study drug administration.
2. Investigational drug use within 28 days of the first dose of pexidartinib.
3. Uncontrolled intercurrent illness.
4. Refractory nausea and vomiting, malabsorption, external biliary shunt, or significant small bowel resection that would preclude adequate absorption.
5. QTcF ≥450 msec (for males) or ≥470 msec (for females) at screening.
6. The presence of a medical or psychiatric condition that, in the opinion of the Principal Investigator, makes the patient inappropriate for inclusion in this study.

10.3 Screen Failures

Patients who sign an informed consent form, are not assigned to a treatment, and do not receive test article are defined as screen failures. For all screen failures, the investigator is to maintain a screening log that documents the screening number, patient initials, and reason(s) for screen failure. A copy of this log should be retained in the investigator's study files.

11.0 PRIOR TREATMENT

Reasonable efforts will be made to determine all relevant treatment received by the patient within 1 month before administration of the test article and within 14 days before test article administration for over-the-counter drugs. All previous treatments for the solid tumor should be recorded. Relevant information must be recorded on the patient's case report form (CRF). This should include the name of the procedure or drug and other information required on the CRF.

12.0 CONCOMITANT TREATMENT

Concomitant treatment is permitted if the medication is not expected to interfere with the evaluation of safety or efficacy of the study drug. During the study, if the use of any concomitant treatment becomes necessary (e.g., for treatment of an adverse event), the treatment must be

recorded on the CRF, including the reason for treatment, generic name of the drug, dosage, route, and date and time of administration.

12.1 CYP3A and UGT Inhibitors

Although pexidartinib does not appear to inhibit CYP drug-metabolizing enzymes to an important extent, caution is warranted when administering pexidartinib to subjects taking drugs that are highly dependent on CYP3A4 for metabolism and have a narrow therapeutic index. It is not known whether systemic exposure to these medications will demonstrate an increase while patients are receiving pexidartinib.

Of the five major CYP isoforms, 3A4 (BFC) may be involved in Phase I metabolism of pexidartinib, with possibly CYP1A2 playing a minor role (see Attachment 5 for a list of common CYP3A4 inhibitors and inducers). In general, strong inducers of CYP3A4 should be avoided unless clinically necessary. These include anticonvulsants, mycin antimicrobials, and antiretrovirals. Some common examples include inducers such as rifampicin, carbamazepine, phenytoin, efavirenz, and nevirapine.

Avoid concomitant use of pexidartinib with moderate or strong CYP3A inhibitors or uridine diphosphate glucuronosyltransferase (UGT) inhibitors. If concomitant use with a moderate or strong CYP3A inhibitor or UGT inhibitor cannot be avoided, reduce the pexidartinib dose according to the recommendations in Table 2. If concomitant use of a moderate or strong CYP3A inhibitor or UGT inhibitor is discontinued, increase the pexidartinib dose (after 3 plasma half-lives of the moderate or strong CYP3A inhibitor or UGT inhibitor) to the dose that was used before starting the inhibitor.

Table 2: Recommended Dosage Reductions for Pexidartinib with Concomitant Use of Moderate or Strong CYP3A Inhibitors or UGT Inhibitors

Current Total Daily Dose	Modified Total Daily Dose	Administration of Modified Total Daily Dose
800 mg	400 mg	200 mg twice daily
600 mg	400 mg	200 mg twice daily
400 mg	200 mg	200 mg once daily

12.2 Hormonal Contraceptives

Pexidartinib has been indicated to be a moderate CYP3A4 inducer, as concurrent administration of pexidartinib decreased the $AUC_{0-\infty}$ of the CYP3A4 substrate midazolam by 57%. As the hormonal contraceptive ethinyl estradiol is a CYP3A4 substrate, there is a potential that exposure of ethinyl estradiol may decrease on concurrent administration with pexidartinib. As pexidartinib may cause embryo-fetal harm when administered to a pregnant woman, females of reproductive potential should be advised to use an effective, non-hormonal method of contraception during treatment with pexidartinib and for one month after the last dose. Males with female partners of reproductive potential should be advised to use an effective method of contraception during

treatment with pexidartinib and for one month after the last dose. Female partners of male patients should concurrently use effective contraceptive methods (hormonal or non-hormonal).

12.3 Acid-reducing Agents

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

13.0 PROCEDURES (DOSE ESCALATION COHORTS)

13.1 Screening Evaluation

Within 21 days (28 days for the one-week run-in patients) before test article administration on study C1D1 (28 days for assessment of tumor burden), all patients will have a screening evaluation that includes the following:

1. Sign and date an IRB/IEC-approved informed consent form before any study-specific screening procedures are performed.
2. Medical history including ethnic origin (Hispanic or non-Hispanic) and race (white, black, Asian, or other).
3. Physical examination including weight (kg) and height (cm).
4. Vital signs (sitting blood pressure, pulse rate, and respiratory rate, and oral temperature [°F]).
5. Standard 12-lead ECG (in triplicate 2 minutes apart) to determine the mean QTc, which must be <450 msec).
6. Recording of concomitant medications.
7. Clinical laboratory evaluation (hematology, chemistry, coagulation, urinalysis, TSH, serum pregnancy test (women of child-bearing potential); see Attachment 1).
8. ECOG Performance status assessment.
9. Baseline assessment of tumor burden (see Attachment 4).
10. Tumor biopsy and/or FDG-PET scan [OPTIONAL].

A patient who meets all of the inclusion criteria will be assigned a patient number. Each patient should fast for 1 hour before and 1 hour after test article administration.

13.2 Run-In Period (Selected Cohorts) – Cycle 1 Day(-7), Day(-6), and Day(-4)

1. All 3 days: Recording of concomitant medications and adverse events.

2. All 3 days: Vital signs (sitting blood pressure, pulse rate, and respiratory rate and oral temperature [°F]).
3. All 3 days: Pre-dose blood sample collection for PK analysis and response biomarkers.
4. C1D(-7): Post-dosing blood collection for PK analysis.

13.3 Pre-Treatment (Baseline): Cycle 1 Day 1

Patients will return to the clinic on C1D1 and will undergo the following procedures:

1. Recording of concomitant medications.
2. Vital signs (sitting blood pressure, pulse rate, and respiratory rate and oral temperature [°F]).
3. Standard 12-lead ECG in triplicate 2 minutes apart.
4. Pre-dose blood sample collection for PK analysis and response biomarkers.
5. Pre-dose morning urine collection for response biomarkers.

13.4 Post-Treatment: Cycle 1 Day 1 and Cycle 1 and Day 2

On C1D1, each patient will receive the assigned dose of test article. AE monitoring will be continuous. Vital signs, ECGs, laboratory evaluations, and PK sample collections will be completed at designated times during the study (see Trial Flow Charts). The blood sample for PK analysis should be collected at the scheduled time, within the windows noted in the PK section. ECG in triplicate will be repeated at 2, 4, and 6 hours after administration of study drug. Pulse and blood pressure will be repeated at 1 and 4 hours post administration of study drug on C1D1. Patients will return to the clinic on the morning of C1D2 prior to dosing on that day for evaluation and blood draw to obtain the predose PK time-point (approximately 12 hours after the previous evening dose for a BID dosing regimen).

13.5 Cycle 1 Day 8 ± 1 Day

Patients will return for evaluation of AEs, concomitant meds, vital signs, physical exam, clinical laboratory values, and collection of serum and morning urine for biomarker assessments. A predose blood sample for PK and as well as predose blood samples for response biomarkers will be obtained, as well as a predose morning urine for response biomarkers (see Trial Flow Charts, pp. 16–20).

13.6 Cycle 1 Day 15 and Cycle 1 Day 16 (± 2 Days)

At the C1D15 visit, AEs, concomitant meds, vital signs, physical exam, and clinical laboratory values will be recorded. Triplicate ECGs will be obtained 2, 4, and 6 hours postdose, and PK

evaluation performed as on C1D1 (see Trial Flow Charts, pp. 16–20). Patients will return to the clinic on the morning of C1D16 prior to dosing on that day for evaluation and blood draw to obtain the predose PK time-point (approximately 12 hours after the previous evening dose for a BID dosing regimen). An on-treatment tumor biopsy and/or FDG-PET scan may be obtained in selected patients.

13.7 Cycle 2 Day 1 (± 7 Days)

On C2D1, evaluations will consist of AEs, concomitant meds, physical exam with vital signs, ECOG performance status assessment, clinical laboratory values, a predose PK time-point, serum/urine collection for biomarkers, and blood collection for circulating tumor cells.

13.8 Continued Dosing

Pexidartinib, at the assigned dose, will be offered to each patient as long as both the patient and investigator agree that it continues to be well tolerated, and there has been no evidence of disease progression. Study visits will occur at approximately 4 week (± 7 days) intervals for assessment of safety (AEs, concomitant meds, physical exam with vital signs, and clinical laboratory values), PK, and ECOG status, and 8 week (± 7 days) intervals (or as clinically indicated) for assessment of tumor response or progression. In addition, in the dose escalation phase, hematology (CBC with differential) will be measured every two weeks after Cycle 1. The mid-cycle values may be provided from a local laboratory.

13.9 Dose Modification (Dose Escalation Cohorts)

Reduction/interruption of dosing for adverse events may take place any time. Below are general guidelines for dosage modification for pexidartinib–related toxicities as well as guidelines for their management.

For toxicities which are considered by the investigator unlikely to develop into serious or life-threatening events (e.g., alopecia, altered taste, etc.), treatment should be continued at the same dose without reduction or interruption. In addition, if any Grade 1 toxicity occurs, treatment should be continued at the original dose without interruption. If drug-related Grade 2 toxicity occurs, the Sponsor should be notified, and the investigator may discontinue or interrupt treatment with pexidartinib if it is considered to be medically appropriate. If dosing is interrupted, treatment at the same dose may be resumed once toxicity is ≤Grade 1.

If Grade 3 or 4 drug-related toxicity occurs, immediate treatment interruption will be followed by a selective dose reduction depending on the types of toxicity, and based on discussion and agreement between the investigator and Sponsor after recovery of the toxicity to at least Grade 1. pexidartinib re-challenge after interruption of dosing may occur only if the investigator and Sponsor agree that it is in the best interest of the patient. In addition, the patient's ECOG performance status must be 0–2. Following re-challenge at a modified dose, study visits will occur at approximately one month intervals for assessment of safety and PK, and two month

intervals for assessment of tumor response or progression. Dosing interruptions longer than 3 weeks should generally result in discontinuation from the study, unless the patient has demonstrated a clinical benefit from therapy and would like to continue dosing with study drug. All adjustments should be made in consultation with the Medical Monitor.

If treatment with pexidartinib is interrupted due to bone marrow toxicity in Cycle 2 and beyond, growth factors may be used. However, growth factors should not be used concomitant with study drug dosing, as it will interfere with the assessment of drug toxicity.

14.0 PROCEDURES (EXTENSION COHORTS)

14.1 Screening Evaluation

Within 21 days before test article administration on study C1D1 (28 days for assessment of tumor burden), all patients will have a screening evaluation that includes the following:

1. Sign and date an IRB/IEC-approved informed consent form before any study-specific screening procedures are performed.
2. Medical history including ethnic origin (Hispanic or non-Hispanic) and race (white, black, Asian, or other).
3. Physical examination including weight (kg) and height (cm).Vital signs (sitting blood pressure, pulse rate, and respiratory rate, and oral temperature [°F]).
4. Standard 12-lead ECG to determine the QTcF, which must be <450 msec (for males) or <470 msec (for females).
5. Recording of concomitant medications.
6. Clinical laboratory evaluation (hematology, chemistry, urinalysis, serum pregnancy test (women of child-bearing potential)
7. ECOG Performance status assessment.
8. Baseline assessment of tumor burden (see Attachment 4).
9. Obtaining archival tumor tissue [OPTIONAL] – this can occur anytime during or after the Screening visit
10. Tumor biopsy and/or FDG-PET scan [OPTIONAL].
11. For patients in the malignant effusion Extension cohort, recording of the number of effusion removal procedures and volume, if appropriate (e.g. paracentesis or thoracentesis) required over the previous 6 months.
12. For the GIST cohort, tumor genotyping results for Kit and PDGFR from a CLIA-certified laboratory should be provided if available.

13. For patients enrolled after the implementation of Amendment 8, dispense six (6) Numeric Rating Scale (NRS) for PVNS Symptoms questionnaires with instructions and reminders to complete the daily questionnaire on an outpatient basis for the 6 consecutive days (Day -6 to Day -1) prior to the next scheduled study visit on C1D1 and to bring the completed questionnaires back at that visit. NOTE: At each of the applicable visits, sites should refrain from providing any interpretation of how the questions should be answered by the patient.

A patient who meets all of the inclusion criteria will be assigned a patient number. Each patient should fast for 1 hour before and 1 hour after test article administration.

14.2 Pre-Treatment (Baseline): Cycle 1 Day 1

Patients will return to the clinic on C1D1 and will undergo the following procedures:

1. Recording of concomitant medications.
2. Vital signs (sitting blood pressure, pulse rate, and respiratory rate and oral temperature [°F]).
3. Pre-dose blood sample collection for PK analysis and response biomarkers.
4. Pre-dose morning (second void, between approximately 7 AM and 10 AM) urine collection for response biomarkers.
5. For patients enrolled after the implementation of Amendment 8, collect the six (6) completed NRS for PVNS Symptoms questionnaires and give the patient another one of the questionnaires to complete predose. NOTE: the NRS for PVNS Symptoms questionnaire to be completed in the clinic is exactly the same as the other 6 daily questionnaires.
6. For patients enrolled after the implementation of Amendment 8, then give the patient the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) questionnaire to complete predose. NOTE: At each of the applicable visits, sites should refrain from providing any interpretation of how the questions should be answered by the patient.

14.3 Post-Treatment: Cycle 1 Day 1

On C1D1, each patient will receive the assigned dose of test article. AE monitoring will be continuous.

14.4 Cycle 1 Day 15 (± 2 days)

At the C1D15 visit, AEs, concomitant meds, vital signs, physical exam, test article compliance, and clinical laboratory values will be recorded. An ECG will be obtained, and PK blood samples

will be obtained predose (AM) and at 1, 2, 4 and 6 hours postdose (for patients who have an afternoon clinic visit, the documentation of dosing and PK sampling times is described in Section 20.1). If obtained at the pre-dose Baseline, a repeat tumor biopsy and/or FDG-PET scan may be obtained.

For patients enrolled after the implementation of Amendment 8, give the patient the NRS for PVNS Symptoms questionnaire to complete predose. Then give the patient the WOMAC questionnaire to complete predose. Then dispense six (6) NRS for PVNS Symptoms questionnaires with instructions and reminders to complete the daily questionnaire on an outpatient basis for the 6 consecutive days (Day -6 to Day -1) prior to the C2D1 study visit and to bring the completed questionnaires back at that visit.

14.5 Cycle 2 Day 1 (± 7 days)

On C2D1, evaluations will consist of AEs, concomitant meds, compliance, physical exam with vital signs, weight, ECOG performance status assessment, clinical laboratory values, a predose PK time-point, and serum/urine collection for biomarkers.

For patients enrolled after the implementation of Amendment 8, collect the six (6) completed NRS for PVNS Symptoms questionnaires and give the patient another one of the questionnaires to complete predose. Then give the patient the WOMAC questionnaire to complete predose. Once all other C2D1 procedures have been completed, dispense six (6) NRS for PVNS Symptoms questionnaires with instructions and reminders to complete the daily questionnaire on an outpatient basis for the 6 consecutive days (Day -6 to Day -1) prior to the next scheduled study visit and to bring the completed questionnaires back at that visit.

14.6 Continued Dosing

14.6.1 Visits through Cycle 40

Pexidartinib, at the assigned dose, will be offered to each patient as long as both the patient and investigator agree that it continues to be well tolerated, and there has been no evidence of disease progression. Study visits will occur at 4-week (± 7 days) intervals for assessment of safety (AEs, concomitant meds, physical exam with weight and vital signs, PK, and clinical laboratory values), compliance, and ECOG status, and 8-week intervals (or as clinically indicated) for radiographic assessment of tumor response or progression. Radiographic assessment of tumor status can be performed every four cycles in patients who complete 15 cycles of treatment and have Cycle 13 and Cycle 15 MRI scans that indicate SD or better per local RECIST v1.1 reading (cycle 19, 23, 27…). For PVNS patients, the Sponsor will receive radiologic images for possible retrospective analysis of treatment response, to be performed by a central vendor. For the malignant effusion cohort, the frequency and volume of on-study fluid removal procedures should be recorded.

For patients enrolled after the implementation of Amendment 8, every four weeks collect the six (6) completed NRS for PVNS Symptoms questionnaires and give the patient another one of the questionnaires to complete predose. Then give the patient the WOMAC questionnaire to complete predose. Once all other procedures have been completed at the visit, dispense six (6) NRS for PVNS Symptoms questionnaires with instructions and reminders to complete the daily questionnaire on an outpatient basis for the 6 consecutive days (Day -6 to Day -1) prior to the next scheduled study visit 4 weeks later and to bring the completed questionnaires back at that visit.

14.6.2 Visits after Cycle 40

Pexidartinib, at the assigned dose, will be offered to each patient as long as both the patient and investigator agree that it continues to be well tolerated, and there has been no evidence of disease progression. Study visits will occur at 12-week (± 7 days) intervals (i.e., every 3 cycles) for assessment of safety (AEs, concomitant meds, physical exam with weight and vital signs, hematology, and chemistry), compliance, and 24-week intervals (i.e., every 6 cycles, or as clinically indicated) for radiographic assessment of tumor response or progression. For patients without ongoing Grade 2 or greater related adverse events, frequency of on-site visits may be extended to every 24 weeks, with remote serum chemistry and hematology as well as a telephone check-in for AEs and con meds and to review remote safety laboratory data performed 12 weeks after each on-site visit; Weight, PE, Vitals, WOMAC, NRS, and IP compliance will not be performed remotely). For PVNS patients, the Sponsor will receive radiologic images for possible retrospective analysis of treatment response, to be performed by a central vendor.

At every on-site visit the six (6) completed NRS for PVNS Symptoms questionnaires will be collected and the patient will be given another one of the questionnaires to complete predose. Then the patient will be given the WOMAC questionnaire to complete predose. Once all other procedures have been completed at the visit, six (6) NRS for PVNS Symptoms questionnaires will be given to the patient with instructions and reminders to complete the daily questionnaire on an outpatient basis for the 6 consecutive days (Day -6 to Day -1) prior to the next scheduled study visit 12 weeks later and to bring the completed questionnaires back at that visit.

14.7 Dose Modification (Extension Cohorts)

Reduction/interruption of dosing for adverse events may take place at any time during the study according to guidelines in Table 3. Dose reductions should occur in increments of 200 mg/day, depending on the toxicity grade, as noted in Table 3. Dose reduction/interruption guidelines for hematologic and nonhematologic treatment-related TEAEs are based on severity. Dose interruptions can be implemented at the discretion of the treating Investigator to manage intolerable or clinically significant toxicity. If a dose interruption is required, study assessments should be performed as scheduled, irrespective of the study drug delay, with the exception of PK assessments, which should be deferred until treatment is resumed. Interruptions due to toxicity

lasting >3 weeks require treatment discontinuation unless the medical monitor approves continuation.

Table 3: Dose Modifications

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

ALT = alanine aminotransferase; ALP = alkaline phosphatase; AST = aspartate aminotransferase; DB = direct bilirubin; GGT = gamma-glutamyl transferase; TB = total bilirubin; ULN = upper limit of normal

[a] Confirm ALP elevations as liver isozyme fraction.

Dose interruptions for Grade 2 non-hematologic toxicity for up to 1 week can be implemented at the discretion of the treating physician to manage intolerable or clinically significant toxicity. No dose reduction is required when resuming treatment.

Liver enzyme abnormalities, including increased transaminase values, have occurred with pexidartinib and should also be managed as described in Table 4.

Re-challenge with a reduced dose of pexidartinib may result in a recurrence of increased serum transaminases, bilirubin, or ALP. Monitor liver tests weekly for the first month after re-challenge.

Table 4: Additional Liver Evaluation

Evaluation	Comments
Increase frequency of testing liver chemistries to twice per week (if Grade 3+), 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 examination 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 patient 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 patient 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 as defined in the protocol 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 (e.g., 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.

14.7.1 Renal Impairment

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

14.8 End of Study/Early Withdrawal (last dose for subjects that enroll in phase 4 continuation study or immediately transition to commercial pexidartinib; last + 30 ± 7 days for all other subjects)

Note: In order to be eligible to participate in the phase 4 PVNS continuation study, subjects must not be withdrawn from PLX108-01 until they are ready to begin screening in the phase 4 continuation study. Screening for the phase 4 continuation study may occur prior to withdrawal from PLX108-01.

Following the last dose of drug, all patients will have the following evaluations:

1. Physical examination including weight (kg) and vital signs (sitting blood pressure, pulse rate, and respiratory rate, and oral temperature [°F]).
2. Standard 12-lead ECG to determine QTcF.
3. Clinical laboratory evaluation (hematology, chemistry, urinalysis, serum pregnancy test (women of child-bearing potential).
4. ECOG Performance status assessment.
5. For patients enrolled after the implementation of Amendment 8, collect the six (6) completed NRS for PVNS Symptoms questionnaires and give the patient another one of the questionnaires to complete predose. NOTE: the NRS for PVNS Symptoms questionnaire to be completed in the clinic is exactly the same as the other 6 daily questionnaires.
6. For patients enrolled after the implementation of Amendment 8, then give the patient the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) questionnaire to complete predose. NOTE: At each of the applicable visits, sites should refrain from providing any interpretation of how the questions should be answered by the patient.
7. Radiographic assessment of tumor burden.
8. Test article compliance.
9. Concomitant medications.
10. Collection of surgical data - If surgical resection of the tumor is performed within 30 days of the last dose of study treatment, details of the surgery and its outcome should be obtained.

14.9 Twelve-week Follow-up (last dose + 12 weeks [+4-week window])

Within +12 weeks (+4 week window) of the last dose of study drug, all patients that don't enroll in the phase 4 continuation study or transition immediately to commercial pexidartinib will have the following study evaluations:

1. Radiographic assessment of tumor burden
2. Collection of surgical data - If surgical resection of the tumor is performed within 12 weeks of the last dose of study treatment, details of the surgery and its outcome should be obtained.

For patients who miss the 30-day and 12-week post-treatment follow-up visit, post-treatment radiographic assessments from any source (e.g., primary care provider) within 24 weeks of last dose are acceptable.

15.0 DISCONTINUATION OF TREATMENT AND WITHDRAWAL OF PATIENTS

The reasons a patient may discontinue or be withdrawn from the study include, but are not limited to, adverse event, disease progression, patient request, protocol violation, patient noncompliance, study termination by the Sponsor, and subject transition to commercial pexidartinib (Turalio™). When a patient discontinues or is withdrawn, the investigator will notify the Sponsor and should perform the procedures indicated in the End of Study visit column in the study flow chart 7–30 days after the last dose of study drug and prior to initiation of any new anti-cancer therapy. Follow-up information will be obtained for patients who discontinue their participation in or are withdrawn from the study. Patients withdrawn from the study will be replaced at the discretion of the medical monitor and the investigator. Test article administration may be discontinued for an adverse event or at the discretion of the investigator.

16.0 TEST ARTICLE

16.1 Test Article Administration

Test article (study drug) will be administered only to patients who have signed and dated an informed consent form. Test article will be administered on days 1 through 28 or longer in the fasting state with 240 mL (8 oz.) of room-temperature water. The patient should fast at least 2 hours before administration and 1 hour after administration of the test article. Patients will be permitted to eat a low-fat snack (e.g., crackers, toast, tea) during the fasting period if needed. Test article will be taken orally by swallowing the capsules. For patients with tumors of the head and neck area who may have difficulty swallowing capsules, test article may be administered by emptying the contents of the dose (e.g., 3 x 200 mg capsules in the morning, and 2 x 200 mg capsules in the evening for a total daily dose of 1000 mg/day) into an empty glass. Approximately 6 ounces of orange juice, apple juice, or cola should be added to the glass, stirred vigorously with a spoon and the patient should drink the contents, add 2 additional ounces to the glass, stir again and drink the remaining contents. The entire dose should be consumed within 30 minutes and the capsule shells should be discarded in a bio-disposable hazard bag provided by the site. NOTE: The Plexxikon Medical Monitor must be consulted prior to implementation of this alternative method of test article administration.

Test article administration will start on C1D1 and should be taken once daily for the initial cohort. Subsequent cohorts may utilize a twice daily dosing regimen, with study drug being administered at approximately 12-hour intervals. On PK collection C1D1 and C1D15, the patients will be administered pexidartinib capsules at the clinical site. The time of the administration will be recorded. On non-PK collection days, patients will administer the study drug at home. Missed doses (i.e., outside of a + 2-hour window) should be skipped and not administered as a double dose at the next administration. Patients who vomit their dose should be instructed to NOT to make up that dose. Patients should take precautions to prevent accidental ingestion of or exposure to investigational drug by family members or other cohabitants.

Food-Effect Assessment:

Once the optimal dose has been identified at steady state (C1D15) in the fasted state, a subset of patients may be studied in this trial to assess the effect of food on pexidartinib exposure. For active patients who consent to this optional procedure, the food-effect assessment will only be initiated on or after the C1D15 visit. C1D15 will remain a fasted PK analysis visit, i.e., PK samples should be obtained in the fasted state at predose (AM) and 1, 2, 4 and 6 hours postdose. After electing to participate in this optional procedure, at their next clinic visit these patients will have PK samples drawn prior to the morning dose and then 2 and 4 hours post-dose in the fasting state (with a low-fat snack if needed, as above). This will serve as a baseline steady state PK assessment of pexidartinib administered in the fasting state. The patients should then be instructed to begin dosing study drug with meals, beginning with the evening dose on the day of this visit (if a BID dosing regimen is being used). Each pexidartinib dose should be taken with food (for example breakfast and dinner). The dose should be administered within 30 minutes of beginning the meal, but not before the meal. The patients will be asked to return to the clinic 2–4 weeks after the food-effect assessment has begun. At this visit, a total of 3 blood samples (predose that morning, 2 and 4 hours post-dosing with a meal) will be drawn for analysis of pexidartinib exposure.

After the effect of food on pexidartinib exposure has been determined, all patients in this trial will be informed whether or not to take study drug with meals.

16.2 Packaging and Labeling

Pexidartinib-HCl capsules (100 mg or 200 mg strength of the active free base of pexidartinib) are manufactured, packaged, and labeled according to GMP and GCP.

16.3 Storage and Stability

Pexidartinib-HCl capsules will be stored at the clinical site, as indicated on the study drug label, i.e., room temperature (not above 25°C).

Patients will be requested to store the pexidartinib at the recommended storage conditions noted on the label out of the reach of children or other cohabitants.

16.4 Dose Escalation

At least three and up to six patients will be enrolled in each dose level using 100% dose increments for each level in the absence of Grade 2 or greater drug-attributable toxicity. In each cohort (and following the one-week run-in period for applicable patients), the first patient will be observed for at least one week before additional patients in that cohort are treated with pexidartinib. Following the one-week run-in period for applicable patients, upon the occurrence of Grade 2 or greater toxicity, in the absence of DLT, dose escalation will proceed sequentially by up to 50% increments. Following the one-week run-in period for applicable patients, if one DLT is observed in one of the first 3 patients during the first cycle in a given cohort, at least 6 patients will be treated at that dose. Following the one-week run-in period for applicable patients, if DLT is observed in 2 or more of 6 patients at a dose level, then the next lower dose level will be expanded or an intermediate dose level will be introduced. Dose escalation will only be permitted if adequate safety and tolerability have been demonstrated at the previous lower dose for 28 days for the first 3 patients. The DLTs observed in all patients in the first cycle will be taken into account when evaluating the safety of a given dose level to support dose escalation or selection of a recommended Phase 2 dose. Dose escalation decisions will be made during teleconferences attended by the medical monitor and appropriate personnel from all participating sites.

Dose Limiting Toxicities during the first 28 days of treatment are defined as follows:

- Any CTCAE (version 4) Grade 4 toxicity (Grade 4 neutropenia for ≥3 days)
- Any CTCAE Grade 3 toxicity other than Grade 3 lymphopenia
- CTCAE Grade 2 vomiting within 2 hours of study drug administration on 3 consecutive days despite optimal anti-emetic therapy
- If, for any reason, either the Principal Investigator or Sponsor deems further dose escalation inappropriate

The specific criterion for Grade 2 vomiting is based on the observations in the dog toxicity studies; vomiting may preclude adequate oral absorption of study drug. The justification for the exemption of Grade 3 lymphopenia is based on the following: a) modest lymphopenia of uncertain mechanism was observed in the 28-day GLP rat repeat dose toxicology study, but only at significant dose and exposure multiples vs. the clinic, b) asymptomatic and clinically nonsignificant lymphopenia is a common finding in patients with advanced solid tumors, c) patients may exhibit continuing or even worsening asymptomatic lymphopenia during clinical trials with no clinical consequence, and d) the clinical risk of G3 lymphopenia, in the absence of concurrent atypical infections, is minimal.

The MTD is defined as the dose at which ≤1 of 6 patients experience a DLT during Cycle 1, with the next higher dose having at least 2 of the up to 6 patients experiencing a DLT during Cycle 1.

No dose reductions are to be made during Cycle 1, which is the primary evaluation period for safety. Dosing will be discontinued based on DLT criteria noted above. If a patient has a documented objective clinical benefit despite having an individual DLT, continued dosing at a reduced dose may be allowed, after consultation with the FDA.

16.5 Test Article Accountability, Reconciliation, and Return

The investigator is accountable for all test article supplied by the Sponsor. The designated copies of the completed dispensing and inventory record will be returned to the Sponsor after the Sponsor has performed accountability procedures.

All test articles must be returned to the Sponsor or contract distribution center with the appropriate form. Unused test article may also be destroyed and documented at the investigative site in accordance with GCP and site SOPs.

16.6 Test Article Compliance

Test article should be administered at each scheduled clinic visit. At each clinic visit, patients will be questioned about their compliance with study drug administration.

17.0 MEASURES TO MINIMIZE/AVOID BIAS

Patients are numbered sequentially. Each patient will be assigned a unique number and will keep this number for the duration of the study. Patient numbers will not be reassigned or reused for any reason. Patients should be identified to the Sponsor only by their assigned number, initials, date of birth, and sex. The investigator must maintain a patient master log.

18.0 SAFETY EVALUATION

Routine safety and tolerability will be evaluated from the results of reported signs and symptoms, scheduled physical examinations, vital sign measurements, 12-lead ECGs (including QTc intervals), and clinical laboratory test results.

Safety data will be reviewed by the investigator and the medical monitor. Safety of pexidartinib will be established after 28 days of dosing at the previous dosage group before the next higher dose is initiated.

More frequent safety evaluations may be performed if clinically indicated or at the discretion of the investigator. All AEs will be recorded from the time the patient receives the first dose of study drug until the patient's End of Study visit.

18.1 Physical Examination

Physical examinations will be performed by a licensed physician, physician's assistant, or nurse practitioner.

18.2 Vital Signs

Vital signs will be measured at the study days and times as noted in the flow charts.

18.3 Electrocardiograms

12-lead ECGs will be recorded at screening to assess study eligibility. Please refer to the flow charts for study days and times. For the dose escalation cohorts only, triplicate ECGs will be obtained. Patients should rest in the supine position for at least 5 minutes before the ECG recording is started. The ECGs should be reviewed promptly by a qualified physician (or physician's assistant, nurse practitioner) and any clinically important finding recorded on the appropriate CRF. The investigator is responsible for providing the interpretation of all ECGs. The results will include heart rate, PR interval, QRS interval, QT interval, and QTc interval.

18.4 Safety Laboratory Determinations

Laboratory evaluations will be performed at each participating site at the study visits as noted in the flow charts. For the dose escalation cohorts, blood for CBC values should be obtained mid-cycle after Cycle 1. Please see Attachment 1 for the specific laboratory tests to be performed.

19.0 BIOMARKER SAMPLES

Plasma and spot urine samples will be obtained as noted in the study flow charts.

Details on the preparation, handling, and shipping of blood samples are covered in the Laboratory Manual.

20.0 PHARMACOKINETIC EVALUATION

20.1 Blood Collection

Venous blood samples will be collected in lithium heparin to measure concentrations of pexidartinib for each PK blood collection.

For QD dosing in the dose escalation cohorts, PK samples will be obtained on C1D1 and C1D15 within 30 minutes before dose administration (predose, time 0) and at 30 minutes, 1, 2, 4, and 8 hours post-dosing. For BID dosing, PK samples will be obtained on C1D1 and C1D15 predose (AM) and 1, 2, 4, and 7 hours postdose. The second dose will be administered, and a PK sample will be obtained 1 hour post the second dose (8 hours post the first dose). Predose samples will be obtained on C1D2, C1D8, and C1D16, and then every 4 weeks during continued dosing. Patients should be informed to refrain from taking study drug until they arrive in the clinic. If a patient experiences a DLT or SAE, a single blood sample for PK analysis should be obtained within 48 hours of the event. Samples will be collected and processed according to the instructions in Attachment 2 and Attachment 3.

In the Extension cohorts, PK samples should be obtained pre-dose on C1D1. On C1D15, the samples should be obtained pre-dose and 1, 2, 4, and 6 hours postdose. During continued dosing, PK samples should be obtained once every 4 weeks (predose). PK sampling will no longer occur beyond C40.

Blood samples for PK analysis should be collected at the requested time but the following sample collection windows will be allowed: ±5 minutes for the 30-minute postdose sample; ±10 minutes for the hour 1 through 4–8 postdose samples; within ±30 minutes of dosing on C1D2, C1D8, and C1D16. The exact time of collection should be noted in the CRFs.

If a patient has an afternoon clinic visit, the patient should be instructed to take his or her AM and PM dose as usual. When the patient arrives at the clinic, the PK blood sample should be obtained even though it will be drawn after the patient's AM dose. The time of the AM dose should be entered on the PK CRF, and a comment should be added to the comment field of the CRF to indicate that the PK sample was collected after the AM dose.

Biological specimen samples for pharmacokinetic analysis must be identified with labels provided by the Sponsor.

20.2 Bioanalytical Methodology

The plasma samples will be analyzed for pexidartinib by using a validated method (high performance liquid chromatography (HPLC) with tandem quadrupole mass spectrometric detection) of appropriate specificity and sensitivity.

21.0 MEASUREMENT OF RESPONSE USING ^{18}FDG PET SCANNING

Patients who consent to PET scanning should be instructed to fast for at least 6 hours (if feasible) prior to ^{18}FDG administration to maintain basal levels of plasma glucose and insulin. They are encouraged to keep drinking water to maintain hydration and limit radiation to the urinary tract. Plasma glucose or glucometer levels will be determined before administration of ^{18}FDG to document euglycemia.

The dose of ^{18}FDG will be administered intravenously according to weight (0.15 mCi/kg, ranging from 3 to 16 mCi) and images will be acquired after approximately 60 minutes distribution time. Images will be obtained over the entire body from the base of the skull to mid-thigh, including brain and extremities when clinically relevant.

^{18}FDG PET emission images will be corrected for attenuation. ^{18}FDG PET scanning should be performed prior to biopsy collection procedure to avoid false positive results.

22.0 TUMOR AND RELATED TISSUE COLLECTION

For patients who consent to this tumor and related tissue collection procedure, paired biopsies (where applicable) will be obtained to assess the effect of pexidartinib on PD endpoints and possibly pexidartinib concentration in the tissue (PK). The tumor lesions or fluids amenable to biopsy or extraction should not be target lesions. Patients will not be excluded from the study on the basis of consenting to biopsy. For patients' safety, soft tissue lesions such as skin or subcutaneous metastases will be preferentially selected for biopsy. Liver metastases will also be eligible for biopsy provided that it is considered feasible and safe in the opinion of a staff interventional radiologist. If there is a change in dose or clinical status after C1D15, one or more additional biopsies may be obtained to assess PD and PK information, in consultation with the Sponsor. If surgical resection of the tumor is performed within 12 weeks of the last dose of study treatment, details of the surgery and its outcome should be obtained. Tumor biopsy tissue may be submitted for biomarker analysis.

Where applicable, core biopsy samples should be obtained with an 18-gauge true-cut needle core biopsy device under ultrasound or computed tomography guidance. For cutaneous or subcutaneous lesions, a punch biopsy may be performed in place of a core biopsy. The tissue samples should be submitted fresh to the surgical pathology laboratory. If feasible, one half should be fixed in 10% buffered formalin and routinely embedded in paraffin, while the other half is to be snap-frozen to –70°C.

For samples including but not limited to pleural, peritoneal, cerebrospinal, or other fluids and tissues, please refer to the Sample Handling and Logistics Manual as well as Attachment 2 and Attachment 3.

For patients who consent to archival tumor tissue acquisition, the sample(s) will be obtained to generate baseline or historical evidence of target relevance.

23.0 PATIENT REPORTED OUTCOME (PRO) QUESTIONNAIRES

Patients enrolled after the implementation of Amendment 8 will complete two patient reported outcome (PRO) instruments: the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC®) and the Numeric Rating Scale (NRS) for PVNS Symptoms questionnaire. These will be completed predose at the clinic on C1D1, C1D15, C2D1, and monthly thereafter (and at every 12-week visit after C40) while continuing study drug administration, and at the End of Study visit. In addition, these patients will complete the NRS for PVNS Symptoms questionnaire on an outpatient basis for 6 consecutive days (Day -6 to Day -1) prior to each monthly clinic visit on C1D1, C2D1, C3D1, etc. (and at every on-site visit after C40) while continuing study drug administration.

The PRO questionnaires will be used to help understand which PVNS symptoms may be most meaningful in terms of improvement for a patient, which symptoms did improve with pexidartinib, and which questions might help best detect between-group differences.

23.1 PRO Instruments

Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC®)

The WOMAC (Attachment 7) is a self-administered 24-item instrument assessing pain, stiffness and difficulty performing daily activities. The WOMAC is focused on assessing issues associated with lower extremity conditions, mainly the knee and hip. All items include a 0–10 point NRS scale; the scale for the pain items (5 items) is 0 "no pain" to 10 "extreme pain", the scale for the stiffness items (2) is 0 "no stiffness" to 10 "extreme stiffness", and the scale for the difficulty performing daily activity items (17) is 0 "no difficulty" to 10 "extreme difficulty."

Numeric Rating Scale (NRS) for PVNS Symptoms

The NRS for PVNS Symptoms instrument is a 5-item self-administered questionnaire to assess the "worst" of each of the symptoms pain, swelling, stiffness, instability and limited motion in the last 24 hours (Attachment 6). A 0–10 NRS is provided for each symptom. For pain, 0 indicates "no pain" and 10 indicates "pain as bad as you can imagine," For the other four symptoms, 0 indicates "no (*symptom*)" and 10 indicates "(*symptom*) worst imaginable", e.g., "swelling – worst imaginable."

24.0 STATISTICAL ANALYSIS

24.1 Safety Analysis

All patients in all cohorts who received study medication will be considered evaluable for safety regardless of their duration of treatment.

The objective of the dose escalation is to determine a dose of pexidartinib for which the rate of DLTs is less than 33%. Safety variables to be analyzed are AEs, laboratory test results (hematology, clinical chemistry, coagulation parameters, and urinalysis), ECG, and vital signs. Adverse event terms recorded on the CRFs will be mapped to preferred terms using the Medical Dictionary for Drug Regulatory Activities (MedDRA®) version 7.1 or higher. All AEs will be summarized for each dose group according to the system organ class and preferred term within the organ class. Adverse events will be tallied for overall frequency (number and percentage of subjects), worst reported severity, and relationship to study drug for each preferred term per subject. Serious adverse events will be similarly summarized. Listings of deaths, SAEs, and AEs leading to early termination of study treatment or premature withdrawal from study will also be provided. In addition, all events meeting the criteria of a DLT will be tabulated as a separate listing by subject and dose group. Laboratory variables will be examined using mean change in value from baseline to scheduled time points for each pexidartinib dose group. Laboratory values

will also be categorized according to their CTCAE (version 4) toxicity grade and tabulated by worst on-study toxicity grade and pexidartinib dose group. The baseline value of a variable is defined as the last value obtained on or before the date and time of the first pexidartinib dose. Concomitant medications will also be summarized.

ECG/QT Analysis:

All ECG information will be listed by patient, including change from baseline for numeric ECG parameters (based on means of the triplicate assessments). Summaries by time-point will be provided for absolute and change from baseline numeric ECG parameters (including categorical summaries for QTc absolute and change from baseline). Plots of mean ECG data and their change from baseline over time will be provided. For each of the time points, the available triplicate QTc values will be averaged for all analyses.

The primary study variable for the QT evaluation will be the study specifically corrected QT interval (QTcS or QTcF or QTcB) change from baseline. The correction formulae for QTc will be estimated based on linear or non-linear regression of predose QT interval data and RR data.

In addition, change from baseline for other ECG variables (QT, RR, heart rate, PR, QRS) will be summarized.

Corrected mean changes from baseline in QTc together with one-sided upper 95% confidence intervals will be derived for each timepoint to interpret the effect of pexidartinib on the QT interval.

The following criteria on baseline measurements will be considered in the analysis of the QT interval. Patients who fall within these criteria may bias the interpretation of pexidartinib effect on QT interval. Data from these patients may be analyzed separately from the general patient population.

- Heart rate (HR) greater than 90 or less than 45 beats per minute
- Sustained systolic blood pressure measurements <90 or >140 mmHg or diastolic blood pressure measurements <50 or >90 mmHg at screening or Day -1
- Any concomitant medications that prolong QT/QTcF interval
- History and/or family history of congenital long QT syndrome or sudden death
- Clinically significant abnormal ECG (e.g., marked QT/QTcF prolongation)
- More than 30 msec difference in two extreme, highest and lowest reads of any baseline QTcF at a specific time point
- Short QTcF (<300 msec) at screening or baseline
- Screening or baseline ECG evidence of atrial fibrillation, atrial flutter, complete right or left bundle branch block, WPW-syndrome, or cardiac pacemaker

- QRS and/or T-wave judged to be unfavorable for a consistently accurate QT measurement at baseline (e.g., indistinct QRS onset, low amplitude T-wave, merged T- and U-waves, prominent U-waves)

24.2 Efficacy Analysis

All patients with measurable disease by RECIST version 1.1 criteria at Baseline who complete at least one post-baseline radiographic assessment or discontinue study medication early due to disease progression will be considered evaluable for efficacy.

Response to treatment according to the RECIST criteria will be reported via descriptive statistics by dose level. The absolute and percent change from baseline for the extent of disease (sum of the longest diameters) will be summarized at each scheduled evaluation using descriptive statistics.

For PVNS patients, the Sponsor will receive radiologic images for possible retrospective analysis of treatment response, to be performed by a central vendor. Methodology of assessment will include RECIST 1.1 and development of other techniques for descriptive and exploratory analysis.

All patients who are eligible for efficacy analyses will be evaluable for progression–free survival, regardless of the presence or absence of measurable disease. Progression-free survival will be calculated for each subject. Progression-free survival is defined as the number of days from the first day of treatment to the date of the first documented disease progression or date of death, whichever occurs first.

For each subject with a response to therapy, duration of response will be calculated. The duration of response is defined as number of days from the date of initial response (confirmed at least 28 days later) to the date of first documented disease progression or death, whichever occurs first. If the information is available, the pre-study stability of disease will also be recorded to assist the interpretation of the on-treatment progression-free survival.

In the event no disease progression or death is documented prior to study termination, analysis cutoff, or the start of confounding anticancer therapy, progress-free survival and duration of response will be censored at the date of last evaluable tumor assessments. In addition, relationships between antitumor activity, pharmacodynamic markers, and drug exposure levels will be explored.

For the malignant effusion cohort, the frequency of effusion removal procedures (e.g., paracentesis or thoracentesis) prior to study entry will be compared to the frequency of on-study fluid removal procedures. The volume of fluid removed by on-study procedures for each patient will be plotted as appropriate. Puncture-free survival (Seimetz 2011) will be calculated for each patient. Puncture-free survival is defined as the number of days from the first day of treatment to the date of the first need for therapeutic puncture or death.

24.3 Pharmacokinetic Analysis

A noncompartmental method of analysis will be used to analyze the plasma concentrations of pexidartinib. C_{max} and the time to attain the C_{max} (t_{max}) will be determined directly from the observed data. The following PK parameters will be estimated, based on available data:

- Clearance
- Volume of distribution
- Area under the plasma/serum concentration-time curve (AUC)
- Elimination half-life

Pharmacokinetic assessments will be measured for each dose cohort of patients with correlations of C_{max} and AUC to any SAEs. Dose-response trends in C_{max} and AUC will be analyzed within each patient group for any suggestion of drug accumulation or alterations in PK based on concomitant medications.

24.4 Pharmacodynamic Analysis

No formal statistical analysis of pharmacodynamic endpoints will be performed. Pharmacodynamic data from each assay will be listed by dose. Possible relationships between PK and pharmacodynamic variables will be explored, as appropriate. Any biological activity will be described.

24.5 Statistical Analyses

Statistical analyses will be descriptive in general. Limited statistical comparisons for a dose effect may be made using analysis of variance. The dependent variables for assessing dose proportionality will be estimates of selected PK parameters.

No formal statistical analysis of data from the PRO instruments will be performed. Results for each instrument will be listed by dose. Change from baseline may be calculated, as appropriate. WOMAC data from patients with only upper extremity disease (e.g., PVNS of the elbow) may be excluded since WOMAC focuses on lower extremity function.

24.6 Sample Size and Power

The primary objective of the study is to assess the safety of pexidartinib in a limited number of patients with solid tumors. The number of patients is not based on statistical power considerations.

For the dose escalation phase of the study, 3 to 6 patients will be accrued per dose level in order to ensure the safety and tolerability. The probabilities of detecting DLTs in this study are shown in Table 5 and Table 6.

Table 5: Probabilities of Detecting DLTs (3 Patients)

Number DLTs in a Cohort of 3 Patients	Incidence of DLTs in Patient Population				
	0.10	**0.20**	**0.30**	**0.40**	**0.50**
0 [a]	0.729	0.512	0.343	0.216	0.125
1 [b]	0.243	0.384	0.441	0.432	0.375
2 or more [c]	0.028	0.104	0.216	0.352	0.500

[a] Number of DLTs leads to advancing to the next cohort.

[b] Number of DLTs leading to enrolling an additional 3 patients in the Cohort.

[c] Number of DLTs leading to stopping the study and defining the MTD.

Table 6: Probabilities of Detecting DLTs (6 Patients)

Number DLTs in a Cohort of 6 Patients	Incidence of DLTs in Patient Population				
	0.10	**0.20**	**0.30**	**0.40**	**0.50**
0	NA	NA	NA	NA	NA
1 [a]	0.177	0.197	0.151	0.093	0.047
2 or more [b]	0.066	0.187	0.290	0.339	0.328

[a] Number of DLTs leading to advancing to the next cohort [Prob (1 in first 3 and 0 in second 3)].

[b] Number of DLTs leading to stopping the study and defining the MTD [Prob (1 in first 3 and 1 in second 3) + Prob (1 in first 3 and 2 in second 3)].

For the five disease-specific Extension cohorts, a sample size of 10 patients is considered the minimum sample size required to test the hypothesis that single agent pexidartinib can provide a clinical benefit in this patient population. For each Extension cohort, we plan to test the hypothesis of no clinical benefit against the hypothesis that at least 30% of patients achieve a clinical benefit. With a sample size of 10 patients per group, we will have 85% power at a 0.10 significance level to declare pexidartinib worthy of further study if at least 2 patients achieve clinical benefit. For this study, clinical benefit is defined as either CR/PR or PFS ≥6 months. If fewer than 2 patients achieve clinical benefit within a disease group, pexidartinib will not be considered worth of further study within that disease. Depending on the response in the 10-patient cohort, the sample size for a specific cohort may be increased by 30 additional patients (to approximately 40 patients total) if those data are determined to be necessary to design additional studies in that indication.

For the miscellaneous Extension cohort, a sample size of 20 patients will be used, as the tumor types are anticipated to be rare. The sample size is not determined by any statistical power considerations. Accordingly, the potential clinical benefit will be evaluated on a per-patient basis. If one or more partial responses are observed in patients in the miscellaneous cohort, additional patients (up to 20 total additional patients) may be recruited if needed to profile the tumor responses in the specific (or related) indications.

25.0 PRECAUTIONS

There is no previous experience with pexidartinib in humans. Although major adverse events are not anticipated, the investigator must proceed with utmost caution. Equipment, supplies, and properly skilled medical personnel must be immediately available for emergency use in the event of an unexpected reaction. Patients must be carefully selected and closely monitored.

For a complete description of preclinical studies reported during clinical studies with pexidartinib, please refer to the pexidartinib Investigator's Brochure.

26.0 ADVERSE EVENTS

For safety information on pexidartinib, refer to the most recent version of the Investigator's Brochure.

26.1 Definitions

An **adverse event** (AE) is any untoward, undesired, or unplanned event in the form of signs, symptoms, disease, or laboratory or physiologic observations occurring in a person given a test article in a clinical study. The event does not need to be causally related to the test article. An AE includes, but is not limited to, the following:

- Any clinically significant worsening of a preexisting condition.
- An AE occurring from overdose (i.e., a dose higher than that indicated in the protocol) of a test article, whether accidental or intentional.
- An AE occurring from abuse (e.g., use for nonclinical reasons) of a test article.
- An AE that has been associated with the discontinuation of the use of a test article.

Any treatment-emergent abnormal laboratory result which is clinically significant, i.e., meeting one or more of the following conditions, should be recorded as a single diagnosis on the adverse event page in the CRF:

- Accompanied by clinical symptoms
- Leading to a change in study medication (e.g., dose modification, interruption or permanent discontinuation)
- Requiring a change in concomitant therapy (e.g., addition of, interruption of, discontinuation of, or any other change in a concomitant medication, therapy or treatment)

A serious adverse event is an AE that:

- Results in death (NOTE: death is an outcome, not an event)
- Is life-threatening.

- Requires inpatient hospitalization or prolongation of an existing hospitalization.
- Results in a persistent or significant disability or incapacity.
- Results in a congenital anomaly or birth defect.
- Additionally, important medical events that may not result in death, be life-threatening, or require hospitalization may be considered SAEs when, based on appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

Disease progression is a study end point and clear progression or worsening of neoplasia should not be reported as an adverse event or serious adverse event. Findings that are *clearly* consistent with the expected progression of the underlying cancer should not be reported as an adverse event, and hospitalizations due to the progression of cancer do not necessarily qualify for a serious adverse event. Sudden and unexplained death should be reported as an SAE. If there is any uncertainty about a finding being due solely to progression of neoplasia, the finding should be reported as an adverse event or serious adverse event as appropriate.

Life-threatening refers to immediate risk of death as the event occurred per the reporter. A life-threatening experience does not include an experience, had it occurred in a more severe form, which might have caused death, but as it actually occurred, did not create an immediate risk of death. For example, hepatitis that resolved without evidence of hepatic failure would not be considered life-threatening, even though hepatitis of a more severe nature can be fatal. Similarly, an allergic reaction resulting in angioedema of the face would not be life-threatening, even though angioedema of the larynx, allergic bronchospasm, or anaphylaxis can be fatal.

Hospitalization is official admission to a hospital. An Emergency Room visit lasting longer than 24 hours should be considered a hospitalization. Hospitalization or prolongation of a hospitalization constitutes criteria for an AE to be serious; however, it is not in itself considered a serious adverse event (SAE). In absence of an AE, a hospitalization or prolongation of a hospitalization should not be reported as an SAE. This is the case in the following situations:

- The hospitalization or prolongation of hospitalization is needed for a procedure required by the protocol. Day or night survey visits for biopsy or surgery required by the protocol are not considered serious.
- The hospitalization or prolongation of hospitalization is part of a routine procedure followed by the center (e.g., stent removal after surgery). This should be recorded in the study file.
- Hospitalization for survey visits or annual physicals falls in the same category.

In addition, hospitalizations planned before the start of the study, for a preexisting condition that has not worsened, do not constitute an SAE.

Disability is defined as a substantial disruption in a person's ability to conduct normal life functions.

If there is any doubt about whether the information constitutes an SAE, the information is treated as an SAE.

Relatedness to study medication will be graded as either "probably", "possibly", or "unlikely", as follows:

Probably—The adverse event:

- Follows a reasonable temporal sequence from drug administration
- Abates upon discontinuation of the drug
- Cannot be reasonably explained by the known characteristics of the patient's clinical state

Possibly—The adverse event:

- Follows a reasonable temporal sequence from drug administration
- Could have been produced by the patient's clinical state or by other modes of therapy administered to the patient:

Unlikely—The adverse event:

- Does not follow a reasonable sequence from drug administration
- Is readily explained by the patient's clinical state or by other modes of therapy administered to the patient

A **protocol-related adverse event** is an AE occurring during a clinical study that is not related to the test article, but is considered by the investigator or the medical monitor (or designee) to be related to the research conditions, i.e., related to the fact that a patient is participating in the study. For example, a protocol-related AE may be an untoward event occurring during a washout period or an event related to a medical procedure required by the protocol.

Other Reportable Information: certain information, although not considered an AE, must be recorded, reported, and followed up as indicated for an AE. This includes:

- A case involving a pregnancy exposure to a test article, unless the product is indicated for use during pregnancy, e.g., prenatal vitamins. Information about use in pregnancy encompasses the entire course of pregnancy and delivery and perinatal and neonatal outcomes, even if there were no abnormal findings. If a pregnancy is confirmed, test article must be discontinued immediately in female patients. All reports of pregnancy must be followed for information about the course of the pregnancy and delivery, as well as the condition of the newborn. When the newborn is healthy, additional follow-up is not needed. Pregnancies occurring up to 3 months after completion of the study treatment must also be reported to the investigator.
- Overdose (e.g., a dose at least 40% higher than that indicated in the protocol). An overdose or incorrect administration of study drug is not an AE unless it results in untoward medical effects. Any study drug overdose or incorrect administration of study drug should be noted on the study drug administration CRF.
- Abuse (e.g., use for nonclinical reasons) with or without an AE.
- Inadvertent or accidental exposure with or without an AE.
- Device malfunction with or without an AE.

26.2 Recording and Reporting

A patient's AE or SAE can occur from the time the patient receives the first dose of study drug until the patient's End of Study visit.

The investigator must follow-up on all drug-related AEs, SAEs, and other reportable information until the events have subsided, returned to baseline, the patient has initiated any other anticancer treatment, or in case of permanent impairment, until the condition stabilizes.

All AE and SAEs must be recorded on source documents. All AEs and SAEs for patients who are not screen failures will be recorded in the CRFs.

AEs should be based on the signs or symptoms detected during the physical examination and on clinical evaluation of the patient. In addition to the information obtained from those sources, the patient should be asked the following nonspecific question: "How have you been feeling since your last visit?" Signs and symptoms should be recorded using standard medical terminology.

Any unanticipated risks to the patients must be reported promptly to the IRB/IEC.

26.3 Serious Adverse Event Reporting

Regardless of causality, all SAEs and follow-up information must be reported to the Synteract safety group within 24 hours of learning of the event by completing the study-specific SAE report form and faxing or e-mailing to the contact information on the form. In the case that fax or e-mail is unavailable, the SAE can be reported to the Medical Monitor (see Section 3.1). As a

reminder, all SAEs should also be promptly entered onto the appropriate eCRF form within SynCapture.

Plexxikon (or designee) will process and evaluate all SAEs as soon as the reports are received. For each SAE received, Plexxikon will make a determination as to whether the criteria for expedited reporting have been met.

Plexxikon (or designee) is responsible for reporting relevant SAEs to the relevant regulatory authorities and participating investigators, in accordance with FDA regulations 21 CFR 312.32, ICH guidelines, European Clinical Trials Directive (Directive 2001/20/EC), and/or local regulatory requirements.

Reporting of SAEs by the investigator to the Institutional Review Board (IRB) or Ethics Committee (EC) will be done in accordance with the standard operation procedures and policies of the IRB/EC. Adequate documentation must be maintained showing that the IRB/EC was properly notified.

27.0 STUDY SUSPENSION, TERMINATION, AND COMPLETION

The Sponsor may suspend or terminate the study or any part of the study at any time for any reason. If the investigator suspends or terminates the study, the investigator will promptly inform the Sponsor and the IRB/IEC and provide them with a detailed written explanation. The investigator will also return all test article, containers, and other study materials to the Sponsor, or destroy the materials at the investigative site. Upon study completion, the investigator will provide the Sponsor, IRB/IEC, and regulatory agency with final reports and summaries as required by regulations. For IND studies, the investigator must submit a written report to the Sponsor and the IRB/IEC within 3 months after the completion or termination of the study.

28.0 INFORMED CONSENT

The investigator will provide for the protection of the patients by following all applicable regulations. These regulations are available upon request from the Sponsor. The informed consent form used during the informed consent process must be reviewed by the Sponsor and approved by the IRB/IEC.

Before any procedures specified in the protocol are performed, a patient must:

- Be informed of all pertinent aspects of the study and all elements of informed consent.
- Be given time to ask questions and time to consider the decision to participate.
- Voluntarily agree to participate in the study.
- Sign and date an IRB/IEC approved informed consent form.

29.0 PROTOCOL AMENDMENTS

Any significant change in the study requires a protocol amendment. An investigator must not make any changes to the study without IRB/IEC and Sponsor approval except when necessary to eliminate apparent immediate hazards to the patients. A protocol change intended to eliminate an apparent immediate hazard to patients may be implemented immediately, but the change must then be documented in an amendment, reported to the IRB/IEC within 5 working days, and submitted to the appropriate regulatory agency in the required time frame. All protocol amendments must be reviewed and approved following the same process as the original protocol.

30.0 QUALITY CONTROL AND ASSURANCE

The Sponsor performs quality control and assurance checks on all clinical studies that it sponsors. Before enrolling any patients in this study, Sponsor personnel and the investigator review the protocol, the investigator's brochure, the CRFs and instructions for their completion, the procedure for obtaining informed consent, and the procedure for reporting AEs and SAEs. A qualified representative of the Sponsor will monitor the conduct of the study. During these site visits, information recorded in the CRFs is verified against source documents.

31.0 DIRECT ACCESS, DATA HANDLING, AND RECORD KEEPING

31.1 Investigator

The investigator will permit study-related monitoring, audits, IRB/IEC review, and regulatory inspections by providing direct access to source data and documents.

All information will be recorded on source documents. All required data will be recorded in the CRFs. All CRF data must be submitted to the Sponsor throughout and at the end of the study.

If an investigator retires, relocates, or otherwise withdraws from conducting the study, the investigator must notify the Sponsor to agree upon an acceptable storage solution. Regulatory agencies will be notified with the appropriate documentation.

31.2 Sponsor

The CRF data is stored in a database and processed electronically. The data are reviewed for legibility, completeness, and logical consistency. Automated validation programs identify missing data, out-of-range data, and other data inconsistencies. The lab data will be processed electronically. Requests for data clarification are forwarded to the investigative site for resolution.

32.0 PRE-STUDY DOCUMENTATION

The investigator must provide the Sponsor with the following documents BEFORE enrolling any patients:

- Completed and signed Form 1572.
- All applicable country-specific regulatory forms.
- Current signed and dated curricula vitae for the investigator, subinvestigators, and other individuals having significant investigator responsibility who are listed on the Form 1572 or equivalent, or the clinical study information form.
- Copy of the IRB/IEC approval letter for the protocol and informed consent. All advertising, recruitment, and other written information provided to the patient must be approved by the IRB/IEC. Written assurance of continuing approval (at least annually) as well as a copy of the annual progress report submitted to the IRB/IEC must also be provided to the Sponsor.
- Copy of the IRB/IEC-approved informed consent document to be used.
- Where applicable, a list of the IRB/IEC members and their qualifications, and a description of the committee's working procedure.
- Copy of the protocol sign-off page signed by the investigator.
- Copy of the current medical license of the principal Investigator and any subinvestigators.
- Fully executed Clinical Trial Agreement.
- Where applicable, a financial disclosure form.
- A written document containing the name, location, certification number, and date of certification of the laboratory to be used for laboratory assays and those of other facilities conducting tests. This document should be returned along with the statement of investigator form. The Sponsor must be notified if the laboratory is changed or if any additional laboratory is to be used.
- List of normal laboratory values and units of measure for all laboratory tests required by the protocol. This is required for each laboratory to be used during the study. The Sponsor must be notified if normal values or units of measurement change.

33.0 RECORDS RETENTION

The investigator shall retain and preserve 1 copy of all data generated in the course of the study, specifically including but not limited to those defined by GCP as essential, for the longer of: (i) 2 years after the last marketing authorization for the study drug has been approved or the Sponsor has discontinued its research with respect to such drug or (ii) such longer period as required by applicable global regulatory requirements. At the end of such period, the investigator shall notify the Sponsor in writing of its intent to destroy all such material. The Sponsor shall have 30 days to respond to the investigator's notice, and the Sponsor shall have a further opportunity to retain such materials at the Sponsor's expense.

34.0 REFERENCES

Plexxikon Pexidartinib (PLX3397) Investigator's Brochure.

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ATTACHMENT 1: LABORATORY TESTS

Hematology

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

Blood Chemistry

Sodium	Triglycerides*
Potassium	Total cholesterol*
Chloride	HDL-cholesterol*
CO2	LDL-cholesterol*
Calcium	Uric acid
Phosphorus	Total and direct bilirubin
Glucose*	Aspartate aminotransferase (AST)
Blood urea nitrogen	Alanine aminotransferase (ALT)
Creatinine	Alkaline phosphatase (AP)
Total protein	Lactate dehydrogenase (LDH)
Albumin	

*Fasting is recommended but not required

Urinalysis (microscopic)

pH	Nitrites
Protein/albumin	Ketones/acetone
Glucose/sugar	Hemoglobin/blood

Coagulation (dose escalation cohorts): Protime (PT), partial thromboplastin time (PTT), and international normalized ratio (INR)

TSH (dose escalation cohorts)

Pregnancy test (β-HCG): women of child-bearing potential

Urine Response Biomarkers (all cohorts): Morning N-Telopeptide of Type I Collagen (NTX) to assess bone mineralization and C-Telopeptide of Type II Collagen (CTX-II) to assess cartilage formation

Serum Response Biomarkers (dose escalation cohorts):

- Bone mineralization: C-Telopeptide of Type I Collagen (CTX), Procollagen Type I Intact N-Terminal Propeptide (P1NP), bone-specific alkaline phosphatase (BAP)

- Macrophage and mast cell activity: Tartrate-resistant acid phosphatase (TRAP 5b), Interleukin-6 (IL-6), Interleukin-1β (IL-1β), Matrix Metallopeptidase-3 (MMP-3), Erythrocyte Sedimentation Rate (ESR), C-Reactive Protein (CRP), CSF-1

Serum Response Biomarkers (Extension cohorts):

- IL-6 and CSF-1

Blood Response Biomarkers (dose escalation cohorts):

- Circulating Tumor Cells (CTCs)
- CD14+/CD16+ monocytes (extension cohorts too)

Because the identification of new response prediction or early response biomarkers of disease activity is a rapidly developing field, the definitive list of analyses remains to be determined, but may include additional markers of inflammatory cells such as macrophages, mast cells, and osteoclasts, in addition to inflammation biomarkers that may be related to Fms or Kit inhibition.

Liver Effect Biomarkers

If there is a Grade 2 or higher ALT or AST elevation (i.e., >3 × ULN) at any time during treatment, the patient should be followed closely as determined by the investigator and Medical Montor. The following liver effect biomarkers are required to be obtained at a frequency determined by the Investigator and Medical Monitor.

- mir122, cytokeratin 18 (full-length and caspase-cleaved), and HMGB1 (native and acetylated)

ATTACHMENT 2: COLLECTION, PREPARATION, AND LABELING OF PLASMA AND OTHER SAMPLES BEING COLLECTED

Please consult the study-specific laboratory manual.

ATTACHMENT 3: INSTRUCTIONS FOR SHIPPING FROZEN SAMPLES

Please consult the study-specific laboratory manual.

ATTACHMENT 4: RECIST CRITERIA VERSION 1.1

Measurability of Tumor at Baseline

Definitions

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

Measurable tumor lesions

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

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

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

Non-measurable tumor lesions

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

Special considerations regarding lesion measurability

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

Bone lesions:

- Bone scan, PET scan or plain films are not considered adequate imaging techniques to measure bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.

- Lytic bone lesions or mixed lytic-blastic lesions, *with identifiable soft tissue components*, that can be evaluated by cross sectional imaging techniques such as CT or MRI can be considered as measurable lesions if the soft tissue component meets the definition of measurability described above.
- Blastic bone lesions are non-measurable.

Cystic lesions:

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

Lesions with prior local treatment:

- Tumor lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, are usually not considered measurable unless there has been demonstrated progression in the lesion. Study protocols should detail the conditions under which such lesions would be considered measurable.

Specifications by methods of measurements

Measurement of lesions

All measurements should be recorded in metric notation, using calipers if clinically assessed. All baseline evaluations should be performed as close as possible to the treatment start and never more than 4 weeks before the beginning of the treatment.

Method of assessment

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

Clinical lesions: Clinical lesions will only be considered measurable when they are superficial and ≥10 mm diameter as assessed using calipers (e.g., skin nodules). For the case of skin lesions, documentation by color photography including a ruler to estimate the size of the lesion is suggested. As noted above, when lesions can be evaluated by both clinical exam and imaging, imaging evaluation should be undertaken since it is more objective and may also be reviewed at the end of the study.

Chest X-ray: Chest CT is preferred over chest X-ray, particularly when progression is an important endpoint, since CT is more sensitive than X-ray, particularly in identifying new lesions. However, lesions on chest X-ray may be considered measurable if they are clearly defined and surrounded by aerated lung. Still, non-contrast CT is preferred over chest X-ray.

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

If prior to enrolment it is known that a patient is not able to undergo CT scans with IV contrast due to allergy or renal insufficiency, the decision as to whether a non-contrast CT or MRI (with or without IV contrast) will be used to evaluate the subject at baseline and follow-up, should be guided by the tumor type under investigation and the anatomic location of the disease. For patients who develop contraindications to contrast after baseline contrast CT is done, the decision as to whether non-contrast CT or MRI (enhanced or non-enhanced) will be performed, should also be based on the tumor type, anatomic location of the disease and should be optimized to allow for comparison to the prior studies if possible. Each case should be discussed with the radiologist to determine if substitution of these other approaches is possible and, <u>if not, the patient should be considered not evaluable from that point forward.</u>

Ultrasound: Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.

Endoscopy, laparoscopy: The utilization of these techniques for objective tumor evaluation is not advised. However, they can be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response or surgical resection is an endpoint.

Tumor markers: Tumor markers alone cannot be used to assess objective tumor response. If markers are initially above the upper normal limit, however, they must normalize for a patient to be considered in complete response. Because tumor markers are disease specific, instructions for their measurement should be incorporated into protocols on a disease specific basis. Specific guidelines for both CA-125 response (in recurrent ovarian cancer) and PSA response (in recurrent prostate cancer), have been published. In addition, the Gynecologic Cancer Intergroup has developed CA125 progression criteria which are to be integrated with objective tumor assessment for use in first-line trials in ovarian cancer.

Cytology, histology: These techniques can be used to differentiate between PR and CR in rare cases if required by protocol (for example, residual lesions in tumor types such as germ cell tumours, where known residual benign tumours can remain). When effusions are known to be a potential adverse effect of treatment (e.g., with certain taxane compounds or angiogenesis inhibitors), the cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment can be considered if the measurable tumor has met criteria for response or stable disease in order to differentiate between response (or stable disease) and progressive disease.

Tumor response evaluation

Assessment of overall tumor burden and measurable disease

To assess objective response or future progression, it is necessary to estimate the overall tumor burden at baseline and use this as a comparator for subsequent measurements. Only patients with measurable disease at baseline should be included in protocols where objective tumor response is the primary endpoint. Measurable disease is defined by the presence of at least one measurable lesion (as detailed above in this Attachment 4). In studies where the primary endpoint is tumor progression (either time to progression or proportion with progression at a fixed date), the protocol must specify if entry is restricted to those with measurable disease or whether patients having non-measurable disease only are also eligible.

Baseline documentation of 'target' and 'non-target' lesions

When more than one measurable lesion is present at baseline all lesions up to a maximum of five lesions total (and a maximum of two lesions per organ) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline.

This means in instances where patients have only one or two organ sites involved a maximum of two (one site) and four lesions (two sites), respectively, will be recorded. Other lesions in that organ will be recorded as non-measurable lesions (even if size is greater than 10 mm by CT scan).

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

Lymph nodes merit special mention since they are normal anatomical structures which may be visible by imaging even if not involved by tumor. Pathological nodes which are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of ≥15 mm by CT scan. Only the short axis of these nodes will contribute to the baseline sum. The

short axis of the node is the diameter normally used by radiologists to judge if a node is involved by solid tumor. Nodal size is normally reported as two dimensions in the plane in which the image is obtained (for CT scan this is almost always the axial plane; for MRI the plane of acquisition may be axial, saggital or coronal). The smaller of these measures is the short axis. For example, an abdominal node which is reported as being 20 mm x 30 mm has a short axis of 20 mm and qualifies as a malignant, measurable node. In this example, 20 mm should be recorded as the node measurement. All other pathological nodes (those with short axis ≥10 mm but <15 mm) should be considered non-target lesions. Nodes that have a short axis <10 mm are considered non-pathological and should not be recorded or followed.

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

All other lesions (or sites of disease) including pathological lymph nodes should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required and these lesions should be followed as 'present', 'absent', or in rare cases 'unequivocal progression.' In addition, it is possible to record multiple non-target lesions involving the same organ as a single item on the case report form (e.g., 'multiple enlarged pelvic lymph nodes' or 'multiple liver metastases').

Response criteria

This section provides the definitions of the criteria used to determine objective tumor response for target lesions.

Evaluation of target lesions

- *Complete Response (CR):* Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.
- *Partial Response (PR):* At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.
- *Progressive Disease (PD):* At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression).
- *Stable Disease (SD):* Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

Special notes on the assessment of target lesions

Lymph nodes: Lymph nodes identified as target lesions should always have the actual short axis measurement recorded (measured in the same anatomical plane as the baseline examination), even if the nodes regress to below 10 mm on study. This means that when lymph nodes are included as target lesions, the 'sum' of lesions may not be zero even if complete response criteria are met, since a normal lymph node is defined as having a short axis of <10 mm. Case report forms or other data collection methods may therefore be designed to have target nodal lesions recorded in a separate section where, in order to qualify for CR, each node must achieve a short axis <10 mm. For PR, SD and PD, the actual short axis measurement of the nodes is to be included in the sum of target lesions.

Target lesions that become *'too small to measure'*: while on study, all lesions (nodal and non-nodal) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (e.g., 2 mm). However, sometimes lesions or lymph nodes which are recorded as target lesions at baseline become so faint on CT scan that the radiologist may not feel comfortable assigning an exact measure and may report them as being 'too small to measure'. When this occurs it is important that a value be recorded on the case report form:

- If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm. If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned and BML (below measurable limit) should be ticked (Note: It is less likely that this rule will be used for lymph nodes since they usually have a definable size when normal and are frequently surrounded by fat such as in the retroperitoneum; however, if a lymph node is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned in this circumstance as well and BML should also be ticked).

This default value is derived from the 5 mm CT slice thickness (but should not be changed with varying CT slice thickness). The measurement of these lesions is potentially non-reproducible, therefore providing this default value will prevent false responses or progressions based upon measurement error.

To reiterate, however, if the radiologist is able to provide an actual measure, that should be recorded, even if it is below 5 mm and in that case BML should not be ticked. (BML is equivalent to a less than sign <)

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

Evaluation of non-target lesions

This section provides the definitions of the criteria used to determine the tumor response for the group of non-target lesions. While some non-target lesions may actually be measurable, they need not be measured and instead should be assessed only qualitatively at the time points specified in the protocol.

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

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

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

Special notes on assessment of progression of non-target disease

The concept of progression of non-target disease requires additional explanation as follows:

When the patient also has measurable disease: **in this setting, to achieve 'unequivocal progression' on the basis of the non-target disease, there must be an overall level of substantial worsening in non-target disease in a magnitude that, even in presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy.** A modest 'increase' in the size of one or more non-target lesions is usually not sufficient to qualify for **unequivocal progression** status. The designation of overall progression solely on the basis of change in non-target disease in the face of SD or PR of target disease will therefore be extremely rare.

When the patient has only non-measurable disease: this circumstance arises in some phase III trials when it is not a criterion of study entry to have measurable disease. The same general concepts apply here as noted above, however, in this instance there is no measurable disease assessment to factor into the interpretation of an increase in non-measurable disease burden. Because worsening in non-target disease cannot be easily quantified (by definition: if all lesions are truly non-measurable) a useful test that can be applied when assessing patients for unequivocal progression is to consider if the increase in overall disease burden based on the change in non-measurable disease is comparable in magnitude to the increase that would be required to declare PD for measurable disease: i.e., an increase in tumor burden representing an additional 73% increase in 'volume' (which is equivalent to a 20% increase diameter in a measurable lesion). Examples include an increase in a pleural effusion from 'trace' to 'large', an increase in lymphangitic disease from localized to widespread, or may be described in protocols as **'sufficient to require a change in therapy'**. If 'unequivocal progression' is seen, the patient should be considered to have had overall PD at that point. While it would be ideal to have

objective criteria to apply to non-measurable disease, the very nature of that disease makes it impossible to do so; therefore the increase must be **substantial**.

New lesions

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

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

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

(18)F-Fluorodeoxyglucose Positron Emission Tomography (FDG-PET)

While FDG-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

- Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.
- No FDG-PET at baseline and a positive FDG-PET at follow-up:
  - If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD.
  - If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan).
  - If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.

Evaluation of best overall response

The best overall response is the best response recorded from the start of the study treatment until the end of treatment taking into account any requirement for confirmation. On occasion a response may not be documented until after the end of therapy so protocols should be clear if post-treatment assessments are to be considered in determination of best overall response. Protocols must specify how any new therapy introduced before progression will affect best response designation. The patient's best overall response assignment will depend on the findings of both target and non-target disease and will also take into consideration the appearance of new lesions. Furthermore, depending on the nature of the study and the protocol requirements, it may also require confirmatory measurement. Specifically, in non-randomised trials where response is the primary endpoint, confirmation of PR or CR is needed to deem either one the 'best overall response'. This is described further below.

Time point response

It is assumed that at each protocol specified time point, a response assessment occurs. Table 7 provides a summary of the overall response status calculation at each time point for patients who have measurable disease at baseline.

When patients have non-measurable (therefore non-target) disease only, Table 8 is to be used.

Missing assessments and not-evaluable designation

When no imaging/measurement is done at all at a particular time point, the patient is not evaluable at that time point. If only a subset of lesion measurements are made at an assessment, usually the case is also considered not evaluable at that time point, unless a convincing argument can be made that the contribution of the individual missing lesion(s) would not change the assigned time point response. This would be most likely to happen in the case of PD.

For example, if a patient had a baseline sum of 50 mm with three measured lesions and at follow-up only two lesions were assessed, but those gave a sum of 80 mm, the patient will have achieved PD status, regardless of the contribution of the missing lesion.

If one or more target lesions were not assessed either because the scan was not done, or could not be assessed because of poor image quality or obstructed view, the Response for Target Lesions should be "Unable to Assess" since the patient is not evaluable. Similarly, if one or more non-target lesions are indicated as 'not assessed', the response for non-target lesions should be "Unable to Assess" (except where there is clear progression). Overall response would be "Unable to Assess" if either the target response or the non-target response is "Unable to Assess" (except where this is clear evidence of progression) as this equates with the case being not evaluable at that time point.

Best overall response: all time points

The *best overall response* will be determined by statistical programming once all the data for the patient is known.

Table 7: Time Point Response: Patients with Targets (+/- Non-Target) Disease

Target Lesions	Non-Target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, NE = inevaluable

Table 8: Time Point Response: Patients with Non-Target Disease Only

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/Non-PD	No	Non-CR/non-PD[a]
Not all evaluated	No	NE
Unequivocal PD	Yes or No	PD
Any	Yes	PD

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, NE = inevaluable

[a] 'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised.

Table 9: Best Overall Response When Confirmation of CR and PR Required

Overall Response First Time Point	Overall Response Subsequent Time Point	BEST Overall Response
CR	CR	CR
CR	PR	SD, PD or PRa
CR	SD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	NE	SD provided minimum criteria for SD duration met, otherwise, NE
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
PR	NE	SD provided minimum criteria for SD duration met, otherwise, NE
NE	NE	NE

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, NE = inevaluable

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

Special notes on response assessment

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

In trials where confirmation of response is required, repeated 'NE' time point assessments may complicate best response determination. The analysis plan for the trial must address how missing data/assessments will be addressed in determination of response and progression. For example, in most trials it is reasonable to consider a patient with time point responses of PR-NE-PR as a confirmed response.

Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as 'symptomatic deterioration'. Every effort should be made to document objective progression even after discontinuation of treatment. Symptomatic deterioration is not a descriptor of an objective response: it is a reason for stopping study therapy. The objective response status of such patients is to be determined by evaluation of target and non-target disease as shown in Table 7, Table 8, and Table 9.

Conditions that define 'early progression, early death and non-evaluability' are study specific and should be clearly described in each protocol (depending on treatment duration, treatment periodicity).

In some circumstances it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends upon this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) before assigning a status of complete response. FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. The use of FDG-PET in this circumstance should be prospectively described in the protocol and supported by disease specific medical literature for the indication. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/sensitivity.

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

ATTACHMENT 5: CYP3A4 INHIBITORS AND INDUCERS

Common CYP3A4 Inhibitors

The following lists describe medications and foods which are common inhibitors of CYP3A4. This list should not be considered all-inclusive. Consult individual drug labels for specific information on a compound's propensity to inhibit CYP3A4.

HIV Protease Inhibitors	Others
indinavir nelfinavir ritonavir saquinavir	amiodarone cimetidine clarithromycin erythromycin fluoxetine fluvoxamine itraconazole ketoconazole mibefradil nefazodone troleandomycin verapamil
Food/Juice	
grapefruit juice	

Common CYP3A4 Inducers

The following lists describe medications which are common inducers of CYP3A4. This list should not be considered all-inclusive. Consult individual drug labels for specific information on a compound's propensity to induce CYP3A4.

HIV Antivirals	Others
efavirenz nevirapine	barbiturates carbamazepine glucocorticoids modafinil Phenobarbital phenytoin rifampin St. John's wort troglitazone rifabutin

ATTACHMENT 6: NUMERIC RATING SCALE (NRS) FOR PVNS SYMPTOMS

NUMERIC RATING SCALE (NRS) FOR PVNS SYMPTOMS

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**

The following questions ask about specific symptoms at the site of your tumor.

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

0	1	2	3	4	5	6	7	8	9	10
No swelling										**Worst imaginable**

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										**Worst imaginable**

Please rate your instability (e.g., giving way, loss of balance) by circling the one number that best describes your instability at its worst in the last 24 hours.

0	1	2	3	4	5	6	7	8	9	10
No instability										**Worst imaginable**

Please rate your limited motion (e.g., can't bend or extend at site of tumor) by circling the one number that best describes your limited motion at its worst in the last 24 hours.

0	1	2	3	4	5	6	7	8	9	10
No limited motion										**Worst imaginable**

ATTACHMENT 7: WESTERN ONTARIO AND MCMASTER UNIVERSITIES OSTEOARTHRITIS INDEX (WOMAC) QUESTIONNAIRE

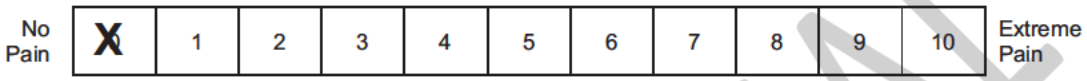
WOMAC® PVNS-GCTTS Index NRS3.1

INSTRUCTIONS TO PATIENTS

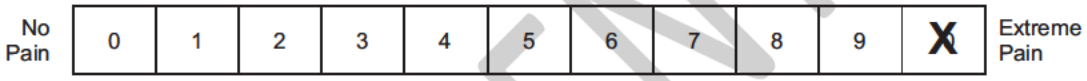
In Sections A, B and C, questions will be asked in the following format and you should give your answers by putting an " **X** " in one of the boxes.

EXAMPLES:

1. If you put your " X " in the box on the far left as shown below, then you are indicating that you have **no** pain.



2. If you put your " X " in the box on the far right as shown below, then you are indicating that you have **extreme** pain.



3. Please note:
   a) that the further to the right you place your " X " the **more** pain you feel.
   b) that the further to the left you place your " X " the **less** pain you feel.
   c) **please do not** place your " X " **outside any of the boxes**.

You will be asked to indicate on this type of scale the amount of pain, stiffness or disability you have felt during the last 48 hours.

Think about your _____ (study joint/tumor location) when answering the questionnaire. Indicate the severity of your pain and stiffness and the difficulty you have in doing daily activities that you feel are caused by the tumor in your _____ (study joint/tumor location).

Your study joint has been identified for you by your health care professional.

If you are unsure which joint is your study joint or are unsure of your tumor location, please ask before completing the questionnaire.

WOMAC® PVNS-GCTTS Index NRS3.1

Section A

PAIN

Think about the pain you felt in your _____ (study joint/tumor location) caused by the tumor during the last 48 hours.

(Please mark your answers by putting an " X " in one of the boxes.)

QUESTION: **How much pain have you had . . .**

1. when walking on a flat surface?

No Pain	0	1	2	3	4	5	6	7	8	9	10	Extreme Pain

2. when going up or down stairs?

No Pain	0	1	2	3	4	5	6	7	8	9	10	Extreme Pain

3. at night while in bed? (that is - pain that disturbs your sleep)

No Pain	0	1	2	3	4	5	6	7	8	9	10	Extreme Pain

4. while sitting or lying down?

No Pain	0	1	2	3	4	5	6	7	8	9	10	Extreme Pain

5. while standing?

No Pain	0	1	2	3	4	5	6	7	8	9	10	Extreme Pain

WOMAC® PVNS-GCTTS Index NRS3.1

Section B

STIFFNESS

Think about the stiffness (not pain) you felt in your (study joint/tumor location) caused by the tumor during the last 48 hours.

Stiffness is a sensation of **decreased** ease in moving your joint.

*(Please mark your answers by putting an " **X** " in one of the boxes.)*

6. How severe has your stiffness been after you first woke up in the morning?

No Stiffness	0	1	2	3	4	5	6	7	8	9	10	Extreme Stiffness

7. How severe has your stiffness been after sitting or lying down or while resting later in the day?

No Stiffness	0	1	2	3	4	5	6	7	8	9	10	Extreme Stiffness

WOMAC® PVNS-GCTTS Index NRS3.1

Section C

DIFFICULTY PERFORMING DAILY ACTIVITIES

Think about the difficulty you had in doing the following daily physical activities caused by the tumor in your (study joint/tumor location) during the last 48 hours. By this we mean **your ability to move around and take care of yourself**.

(Please mark your answers by putting an " X " in one of the boxes.)

QUESTION: **How much difficulty have you had . . .**

8. when going down the stairs?

No Difficulty	0	1	2	3	4	5	6	7	8	9	10	Extreme Difficulty

9. when going up the stairs?

No Difficulty	0	1	2	3	4	5	6	7	8	9	10	Extreme Difficulty

10. when getting up from a sitting position?

No Difficulty	0	1	2	3	4	5	6	7	8	9	10	Extreme Difficulty

11. while standing?

No Difficulty	0	1	2	3	4	5	6	7	8	9	10	Extreme Difficulty

12. when bending to the floor?

No Difficulty	0	1	2	3	4	5	6	7	8	9	10	Extreme Difficulty

13. when walking on a flat surface?

No Difficulty	0	1	2	3	4	5	6	7	8	9	10	Extreme Difficulty

WOMAC® PVNS-GCTTS Index NRS3.1

DIFFICULTY PERFORMING DAILY ACTIVITIES

Think about the difficulty you had in doing the following daily physical activities caused by the tumor in your (study joint/tumor location) during the last 48 hours. By this we mean **your ability to move around and take care of yourself**.

(Please mark your answers by putting an " X " in one of the boxes.)

QUESTION: **How much difficulty have you had . . .**

14. getting in or out of a car, or getting on or off a bus?

No Difficulty	0	1	2	3	4	5	6	7	8	9	10	Extreme Difficulty

15. while going shopping?

No Difficulty	0	1	2	3	4	5	6	7	8	9	10	Extreme Difficulty

16. when putting on your socks or panty hose or stockings?

No Difficulty	0	1	2	3	4	5	6	7	8	9	10	Extreme Difficulty

17. when getting out of bed?

No Difficulty	0	1	2	3	4	5	6	7	8	9	10	Extreme Difficulty

18. when taking off your socks or panty hose or stockings?

No Difficulty	0	1	2	3	4	5	6	7	8	9	10	Extreme Difficulty

19. while lying in bed?

No Difficulty	0	1	2	3	4	5	6	7	8	9	10	Extreme Difficulty