A Phase 1/2 Study of FPA008, an anti-CSF1 Receptor Antibody, in Patients with Pigmented Villonodular Synovitis (PVNS)/ Diffuse Type Tenosynovial Giant Cell Tumor (dt-TGCT)

Protocol Number:	FPA008-002
Investigational Product:	FPA008
IND Number:	125117
Development Phase:	Phase 1/2
Indication Studied:	Pigmented Villonodular Synovitis (PVNS)/Diffuse Type Tenosynovial Giant Cell Tumor (dt-TGCT)
Protocol Version:	5 – Amendment 4
Date of Protocol:	**24 August 2016**
Supersedes:	*Version 4, Amendment 3, dated 09 June 2016*
Sponsor:	Five Prime Therapeutics, Inc. (FivePrime) [redacted]
Responsible Medical Officer:	[redacted]

Confidential

This document contains proprietary and confidential information of Five Prime Therapeutics, Inc. and may not be reproduced or disclosed in whole or in part without written authorization from Five Prime Therapeutics, Inc.

Protocol Approval Signature Page

Declaration of Sponsor

A Phase 1/2 Study of FPA008, an anti-CSF1 Receptor Antibody, in Patients with Pigmented Villonodular Synovitis (PVNS)/Diffuse Type Tenosynovial Giant Cell Tumor (dt-TGCT)

The study will be conducted according to the protocol and in compliance with Good Clinical Practice (GCP), the Declaration of Helsinki, and other applicable regulatory requirements. Essential study documents will be archived in accordance with applicable regulations.

This study protocol was subjected to critical review. The information it contains is consistent with current knowledge of the risks and benefits of the investigational product, as well as with the moral, ethical, and scientific principles governing clinical research as set out in the Declaration of Helsinki, 1989, and the International Conference on Harmonization (ICH) guidelines on GCP.

Declaration of the Investigator

A Phase 1/2 Study of FPA008, an anti-CSF1 Receptor Antibody, in Patients with Pigmented Villonodular Synovitis (PVNS)/Diffuse Type Tenosynovial Giant Cell Tumor (dt-TGCT)

All documentation for this study that is supplied to me and that has not been previously published will be kept in the strictest confidence. This documentation includes this study protocol, Investigator's Brochure (IB), electronic case report forms (eCRFs), and other scientific data.

The study will not be commenced without the prior written approval of a properly constituted Institutional Review Board (IRB) or Independent Ethics Committee (IEC). No changes will be made to the study protocol without the prior written approval of the Sponsor and the IRB or IEC, except as necessary to eliminate an immediate hazard to the patients.

I have read and understood and agree to abide by all the conditions and instructions contained in this protocol.

Principal Investigator's Signature	Date
Name (printed)	
Institution or Company Name	

Protocol Synopsis

Title: A Phase 1/2 Study of FPA008, an anti-CSF1 Receptor Antibody, in Patients with Pigmented Villonodular Synovitis (PVNS)/Diffuse Type Tenosynovial Giant Cell Tumor (dt-TGCT)

Protocol Number: FPA008-002

Clinical Phase: 1/2

Sponsor: Five Prime Therapeutics, Inc.

Study Centers: Approximately 11 study centers in North America, Europe, and Asia

Objectives:

Primary:

- Phase 1: To determine the recommended dose (RD) of FPA008 in patients with pigmented villonodular synovitis (PVNS)/diffuse type tenosynovial giant cell tumor (dt-TGCT)
- Phase 2: To estimate the objective response rate (ORR = CR+PR) of FPA008 in patients with PVNS/dt-TGCT

Secondary:

- To characterize the safety and tolerability of FPA008 in patients with PVNS/dt-TGCT
- To determine the duration of response in responding patients
- To assess the pharmacokinetics of FPA008 in patients with PVNS/dt-TGCT

Exploratory:

- [redacted]
- To evaluate synovial fluid for FPA008 concentration and changes in cellularity in selected patients
- To assess functional outcomes as measured by:
  - Ogilvie-Harris score developed specifically for PVNS (Ogilvie-Harris 1992, Rhee 2010)
  - Brief Pain Inventory (Appendix 5)
  - Joint Stiffness Numeric Rating Scale (Appendix 6)

Study Design: This is a Phase 1/2 study. Phase 1 is a dose escalation, open-label, safety, tolerability, PK and PD study of FPA008. Patients will be enrolled into either Phase 1 or Phase 2 of the study, but not both.

After an initial Screening period of up to 28 days, patients will be treated with FPA008 every 2 weeks in 28-day cycles.

In Phase 1, each dosed patient will be observed during Cycle 1 for safety assessments and occurrence of dose-limiting toxicities (DLT Observation Period). If a patient does not receive 2 doses in Cycle 1 and has not experienced a dose limiting toxicity, then a replacement patient will be necessary at that dose level.

Additional treatments may be administered every 2 weeks in 28-day cycles thereafter as clinically indicated (Extended Treatment Period).

In Phase 2, patients will be treated with FPA008 every 2 weeks in 28-day cycles at a RD selected after assessment of data obtained in Phase 1.

Phase 1: Dose-Escalation

In Phase 1, three dose cohorts are anticipated, with a minimum of 3 patients enrolled in each cohort. The planned dose levels and schedules are:

Dose level 1: 1 mg/kg FPA008 q2w

Dose level 2: 2 mg/kg FPA008 q2w

Dose level 3: 4 mg/kg FPA008 q2wReview of safety, PK and PD profiles may inform decisions to add cohorts with alternative dose levels or dose regimens (e.g., different dosing frequency, higher dose levels) in order to reach an optimal target exposure.

All dose escalation decisions will be based on the assessment of DLTs, overall safety, and tolerability and will be made after the last patient enrolled in each cohort has completed the first treatment cycle. Dose escalation decisions will be agreed upon by the Cohort Review Committee (CRC), consisting of the Sponsor and Investigators.

The following algorithm will be used for dose escalation decisions:

Number of Patients with DLTs	Action
0/3	Open next cohort
1/3	Enroll 3 more patients in same cohort
≥ 2/3	Stop enrollment. Enter 3 more patients at dose level below, if only 3 were previously entered
1/6	Open next cohort
≥ 2/6	Stop enrollment. Enter 3 more patients at a dose level below or at an intermediate dose level if the current dose level is ≥50% higher than the previous dose level

Study Design (Cont.):

The selection of the RD will be based on clinical response and safety data as well as PK and PD profiles. The Sponsor and Investigators may decide to discontinue dose escalation before reaching the highest planned dose of 4 mg/kg or, potentially, evaluate a higher (>4mg/kg) dose if the safety, PK, and PD data support evaluation of different dose levels.

After declaring the RD, the Sponsor and Investigators may decide to evaluate alternative dose levels to those defined in the protocol if the safety, PK, PD, and efficacy data support further evaluation of additional doses in order to reach an optimal target exposure. The dose escalation rules specified in Section 3.1.2 will apply to the additional cohorts.

Phase 1: Extended Treatment Period

On completion of Cycle 1 (Safety and PK Assessment Period), Phase 1 patients may participate in an Extended Treatment Period, which begins on Day 1 of Cycle 2. FPA008 will be administered every 2 weeks in 4-week cycles for up to 24 weeks of treatment or until disease progression (if before 24 weeks of treatment), unacceptable toxicity, patient or physician decision to discontinue, or termination of the study.

Phase 2

Enrollment in Phase 2 will begin when the RD has been identified by the CRC, based on overall safety, tolerability, objective response, PK, PD and estimates of efficacious exposures extrapolated from nonclinical data. If dose escalation continues higher than 4 mg/kg, the RD may or may not be a maximum tolerated dose (MTD), if an MTD is identified in Phase 1. For example, if an MTD is not reached, or if exposure at the MTD is much higher than the level believed to be required for efficacy, or if subsequent cycles of treatment provide additional insight on the safety profile, then the RD may be a different, though not higher, dose than the MTD.

After initiation of Phase 2, the RD may be changed based on data from continued dose exploration. Any change in the RD for Phase 2 will only apply to newly enrolled patients. There will be no intra-patient dose escalation. The total number of patients for enrollment in Phase 2 will be approximately 25-30, irrespective of the assigned dose.

Treatment is planned to continue for up to 24 weeks.

If a patient appears to have stable or improving symptoms with stable measurable disease or better by MRI (magnetic resonance imaging), but is having intolerable or Grade 3 or greater adverse events, dose reduction by 25-50% may be allowed with Sponsor agreement.

Retreatment Cohort

At the discretion of the Sponsor, patients from the 1 mg/kg or 2 mg/kg cohorts may be retreated at the RD after a washout period of at least 4 months and rescreening. These patients may be treated at the RD for an additional 6 cycles (12 doses).

Number of Patients:

Phase 1: Approximately 12 - 15 patients

Phase 2: Approximately 25-30 patients

Retreatment Cohort: Up to 5 patients from the 1 mg/kg and 2 mg/kg cohorts from Phase 1 who completed 6 cycles of treatment may be enrolled at the Sponsor's discretion.

Study Population:

Inclusion Criteria

Patients enrolling into Phase 1 or Phase 2 must meet ***all*** of the following inclusion criteria:

1. Understand and sign an Institutional Review Board/Independent Ethics Committee-approved informed consent form prior to any study-specific evaluation
2. Age ≥18 years
3. Histologically confirmed diagnosis of inoperable PVNS/dt-TGCT or potentially resectable tumor that would result in unacceptable functional loss or morbidity as determined by a qualified surgeon or multi-disciplinary tumor board (must be documented in the CRF during screening)
4. Measurable PVNS/dt-TGCT by RECIST 1.1 on MRI
5. ECOG performance status ≤1
6. Willing and able to comply with all study procedures
7. In sexually-active patients (i.e., females of childbearing potential, who have not undergone menopause as defined by 12 consecutive months of amenorrhea or had a permanent sterilization procedure and males, who have not had a permanent sterilization procedure), willingness to use 2 effective methods of contraception, of which one must be a physical barrier method (condom, diaphragm, or cervical/vault cap) until 6 months after the last dose of FPA008. Other effective forms of contraception are permanent sterilization (hysterectomy and/or bilateral oophorectomy, or bilateral tubal ligation with surgery, or vasectomy) at least 6 months prior to Screening. Females <55 years of age should have FSH >40. Female patients of childbearing potential must be on stable oral contraceptive therapy or intrauterine or implant device for at least 90 days prior to the study, or abstain from sexual intercourse as a way of living.

Patients enrolling in the retreatment cohort of the study must also meet the following inclusion criteria:

8. Completed 6 cycles of initial treatment at the1 mg/kg or 2 mg/kg dose levels and the end-of-treatment follow-up period.

   ***Note*:** Prior to re-treatment, potential patients in this retreatment cohort will be re-assessed to ensure they meet the same eligibility requirements as untreated patients.

No waivers of these inclusion criteria will be granted.

Study Population (Cont.):

Exclusion Criteria

Patients enrolling into Phase 1 or Phase 2 will be excluded if any of the following criteria apply:

1. Prior therapy with an anti-CSF1R antibody (with the exception of patients previously treated with FPA008 who will be enrolled in the Retreatment Cohort)
2. Prior therapy with PLX3397 unless discontinued for intolerance (i.e., non-progression on prior kinase inhibitor); prior therapy with imatinib or nilotinib is allowed
3. CK and liver function tests (including AST, ALT, and total bilirubin), outside of the range of local laboratory normal at Screening
4. Inadequate organ or bone marrow function defined as: hemoglobin <10 g/dL, absolute neutrophil count <1.5x 10^9/L, platelet count <100x 10^9/L, serum creatinine >1.5x ULN or calculated creatinine clearance <30 mL/min
5. Any surgical procedure of the involved joint within 12 weeks prior to first study dose administration (except baseline synovium biopsy, if performed)
6. Current or history of clinically significant muscle disorders (e.g., myositis), recent unresolved muscle injury, or any condition known to elevate serum CK levels
7. History of congestive heart failure or myocardial infarction <1 year prior to first study dose administration
8. Decreased cardiac function with NYHA > Class 2
9. Uncontrolled or significant heart disorder such as unstable angina
10. Significant abnormalities on ECG at Screening. QTcF >450 msec for males or >470 msec for females at Screening
11. Contraindications to MRI and use of intravenous gadolinium-based contrast agents
12. History of severe allergic, anaphylactic, or other infusion related reaction to a previous biologic agent
13. Treatment with any anticancer therapy or participation in another therapeutic clinical study with investigational drugs ≤ 28 days prior to first dose of FPA008
14. Known history of ADAs to previous biologic agents
15. Known history of sensitivity to Tween 20 (polysorbate 20)
16. Consumption of non-pasteurized milk on a regular basis, or known significant risk of exposure to opportunistic intracellular infections such as *listeria,* or other such pathogens.

Study Population (Cont.):

17. Receipt of any vaccine within 28 days prior to first day of treatment. The effect of FPA008 on mounting an immunologic vaccine response is not known. Flu or other vaccinations may be administered while on study but the impact of FPA008 on the safety and efficacy of the vaccination is unknown.
18. Current unresolved infection or chronic active clinically significant infection (viral [e.g., HBV, HCV], bacterial, fungal, or other) which in the opinion of the Investigator would place the patient at risk from exposure to a CSF1R inhibitor
19. Known positive test for human immunodeficiency virus (HIV)
20. Active TB
21. Positive test for latent TB at Screening (Quantiferon test)
22. History of prior malignancy, except:
    - Curatively treated non-melanoma skin malignancy
    - Cervical cancer *in situ*
    - Solid tumor treated curatively more than 2 years previously without evidence of recurrence
23. Lack of peripheral venous access or any condition that would interfere with drug administration or collection of study samples
24. Any uncontrolled medical condition or psychiatric disorder which in the opinion of the Investigator would pose a risk to patient safety or interfere with study participation or interpretation of individual patient results
25. Inability to perform and/or comply with study and follow-up procedures
26. Known history of metastatic PVNS/dt-TGCT

No waivers of these exclusion criteria will be granted.

Dose-Modification Criteria:

Dose reductions may be permitted for patients on treatment beyond the DLT period in Phase 1 or any patient in Phase 2 upon discussion with and approval by the Sponsor.

Patients may miss up to 2 consecutive doses (up to 6 weeks between doses) for adverse or other events; omission of additional dosing longer than 6 weeks for adverse or other events will necessitate the patient's removal from the study unless allowed by the Sponsor.

If a patient's dose is decreased for an adverse event, dose escalation to the originally assigned dose may occur after resolution of the AE and after discussion with and approval by the Sponsor. Recurrence of the AE to greater than Grade 2 will result in permanent dose reduction without the opportunity for re-escalation.

Concomitant Medications:

Supportive care (e.g., anti-emetics; analgesics for pain control) may be used at the Investigator's discretion and in accordance with institutional procedures.

Withdrawal Criteria:

A patient must be discontinued from protocol-prescribed therapy if any of the following apply:

- Consent withdrawal at the request of the patient or their legally authorized representative
- Progression of patient's disease.
- Any event that would pose an unacceptable safety risk to the patient
- A concurrent illness that would affect assessments of the clinical status to a significant degree
- A positive pregnancy test at any time during the study
- At the specific request of the Sponsor or its authorized representative (e.g., if the study is terminated for reasons of patient safety).

PK and PD Assessments:

Pharmacokinetics (PK)

The following PK parameters will be derived from concentration-time data for FPA008, when appropriate and applicable (other parameters, such as accumulation ratio and half-life, may also be calculated):

- Area under serum concentration-time curve (AUC)
- Maximum serum concentration (C_{max})
- Minimum serum concentration (C_{min})
- Clearance (CL)
- Volume of distribution at steady state (V_{ss})

Pharmacodynamics (PD)

- [redacted]
- Synovial fluid (optional)
  - FPA008 concentration; cellular component for above markers by IHC

Immunogenicity

Blood samples will also be collected to assay for anti-drug antibodies (ADA) to FPA008.

Tumor Response Parameters:	MRI of affected joints will be performed at Screening, 4, 8, and 16 weeks (or until treatment discontinuation) following the start of treatment. A tumor assessment should also be performed at the 30 days (±7 days) and 90 days (±7 days) End of Treatment Follow-Up Visits unless already performed within the previous 6 weeks. Response per MRI will be assessed using RECIST 1.1 and TVS based on independent central radiology review. Clinical assessment of health outcomes (function, symptoms) will be done at Screening, C1D15 (pre-dose), C2D1 (pre-dose), and then on Day 1 (pre-dose) for all subsequent cycles through 24 weeks of treatment or until treatment is discontinued. Patients who have not progressed should continue onto Long-Term Follow-up after completing the End of Treatment Follow-up Period. Patients are to be followed (MRI and assessment of health outcomes) every 14 (± 2) weeks until progression, the patient undergoes local therapy (e.g., resection, radiation) or a new systemic therapy is initiated, for up to 52 weeks following C1D1. Positron emission tomography (PET) scans will be performed for a subset of approximately 10 patients from Phase 2 at Screening, C3, D1 (±7 days), C6D15 (±7 days) Visit, 90 days (±7 days) End of Treatment Follow-Up Visit, and at the first Long-Term Follow-up Visit (14 weeks (± 2 weeks) post 90 days End of Treatment Visit).
Safety Assessments:	Safety of FPA008 will be assessed by monitoring adverse events and changes in physical examinations, vital signs, 12-lead ECGs, and clinical laboratory measurements.
Statistical Procedures:	All analyses will be descriptive and will be presented by dose group and overall as appropriate. Patient data from the Phase 2 will be summarized as a separate group. All patients dosed at the RD will also be summarized. Because of the low number of patients that may be enrolled at lower dose levels, some dose levels may be combined for summarization. Missing values in the efficacy data will be treated as missing; no efficacy data will be imputed. Data collected in this study will be presented using summary tables and patient data listings. Continuous variables will be summarized using descriptive statistics, specifically the mean, median, standard deviation (SD), minimum, and maximum. Categorical variables will be summarized by frequencies and percentages. 95% confidence intervals will be presented where appropriate. Response rates and the corresponding confidence interval (CI) will be used to access efficacy. It is anticipated that there will be a total of approximately 20-30 patients treated at the RD overall. Table 8 displays the corresponding 95% confidence interval and the precision for various sample sizes and observed response rates. PK parameters will be calculated using non-compartmental analysis methods, though compartmental analysis methods may be employed if appropriate.

List of Key Study Personnel

Sponsor:

[redacted]

Contract Research Organization:

[redacted]

Serious Adverse Event Reporting:

[redacted]

Table of Contents

Tables in Text

List of Appendices

List of Abbreviations and Definitions

ADA	Anti-drug antibody
ADCC	Antibody-dependent cell-mediated cytotoxicity
AE	Adverse event
ALT	Alanine transaminase
ANC	Absolute neutrophil count
APTT	Activated Partial Prothrombin Time
AST	Aspartate transaminase
AUC	Area under serum concentration-time curve
β-HCG	Beta-human chorionic gonadotropin
BPI	Brief Pain Inventory
BUN	Blood urea nitrogen
CBC	Complete blood count
CK	Creatinine kinase
C_{max}	Maximum serum concentration
C_{min}	Minimum serum concentration
CL	Clearance
CO_2	Carbon dioxide (bicarbonate)
CR	Complete response
CRC	Cohort Review Committee
CRO	Contract research organization
CSF1	Colony stimulating factor-1
CT	Computed tomography
CTx	Collagen-type I C-terminal telopeptide
CTCAE	Common Terminology Criteria for Adverse Events
DILI	Drug Induced Liver Injury
DLT	Dose-limiting toxicity
dt-TGCT	Diffuse type tenosynovial giant cell tumor
eCRF	Electronic case report form
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
HIV	Human immunodeficiency virus

IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IHC	Immunohistochemistry
IND	Investigational New Drug (application)
INR	International normalized ratio
IRB	Institutional Review Board
IV	Intravenous
LDH	Lactate dehydrogenase
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
MCV	Mean corpuscular volume
MRI	Magnetic resonance imaging
MTD	Maximum tolerated dose
NCI	National Cancer Institute
NOAEL	No observed adverse effect level
NTX	N-terminal telopeptide
NYHA	New York Heart Association
ORR	Objective response rate
PD	Progressive disease
PD	Pharmacodynamic
PET	Positron emission tomography
PFS	Progression free survival
PK	Pharmacokinetic
PR	Partial response
PRO	Patient reported outcome
PS	Performance status
PT	Prothrombin time
PVNS	Pigmented villonodular synovitis
QTc	Corrected QT interval
RBC	Red blood cell
RD	Recommended dose
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	Serious adverse event
SAP	Statistical analysis plan

SD	Stable disease
SUV	Standardized uptake value
$t_{1/2}$	Half-life
TB	Tuberculosis
TRAP5b	Tartrate resistant acid phosphatase 5b
TVS	Tumor volume score
ULN	Upper limit of normal
V_{ss}	Volume of distribution at steady state
WBC	White blood cell

1. Introduction

1.1. PVNS Background

Pigmented villonodular synovitis (PVNS) is a benign neoplasm of the synovium with features of both reactive inflammation and clonal neoplastic proliferation in which colony stimulating factor-1 (CSF1) is over expressed. A common translocation of the *CSF1* gene (1p13) to the *COL6A3* promoter (2q35) is present in approximately 60% of PVNS patients. The translocation is accompanied by CSF1 overexpression in the synovium. In addition, approximately 40% of PVNS patients have CSF1 overexpression in the absence of an identified *CSF1* translocation. The consistent presence of CSF1 overexpression in all cases of PVNS and reactive synovitis suggests both an important role for CSF1 in the spectrum of synovial pathologies and the utility of targeting the CSF1/CSF1R interaction therapeutically (West 2006).

In PVNS, CSF1 overexpression is present in a minority of synovial cells, whereas the majority of the cellular infiltrate expresses CSF1R but not CSF1. This has been characterized as a tumor-landscaping effect with aberrant CSF1 expression in the neoplastic cells, leading to the abnormal accumulation of non-neoplastic cells that form a mass.

Surgery is the treatment of choice for patients with localized PVNS. Recurrences occur in 8-20% of patients and are easily managed by re-excision. PVNS/dt-TGCT tends to recur more often (33–50%) and has a much more aggressive clinical course. Patients are often symptomatic and require multiple surgical procedures during their lifetime. For patients with unresectable disease or multiple recurrences, systemic therapy using CSF1R inhibitors may help delay or avoid surgical procedures and improve functional outcomes (Ravi 2011).

Imatinib, a non-specific inhibitor of CSF1R, has undergone evaluation in 29 PVNS patients. The median age was 41 years and the most common site of disease was the knee (n = 17; 59%). Five of 27 evaluable patients had complete (n=1) or partial (n=4) responses per RECIST for an overall response rate of 19%. Twenty of 27 patients (74%) had stable disease. Symptomatic improvement was noted in 16 of 22 patients (73%) who were assessable for symptoms. Despite a high rate of symptomatic improvement and an overall favorable safety profile, 10 patients discontinued treatment for either toxicity or other reasons (Cassier 2012).

Recently two studies of potent inhibitors of CSF1 signaling have shown preliminary but compelling clinical activity in patients with PVNS. PLX3397, a CSF1R kinase inhibitor, and RG7155, a monoclonal antibody targeting CSF1R have been evaluated in patients with PVNS (Cassier 2014, Tap 2014). In both studies, a majority of patients with PVNS responded to treatment based on RECIST, FDG-PET, and/or total volume score, which is a measure of disease volume by MRI.

In PVNS, overexpression of CSF1 by a minority of cells leads to recruitment of CSF1R-expressing cells that make up the bulk of the tumor mass. FPA008 antagonizes CSF1R activation and should result in the reduction of CSF1R-expressing cells in the tumor thereby providing clinical benefit.

1.2. FPA008: Description of the Molecule

[redacted]

1.2.1. Nonclinical Studies with FPA008

1.2.1.1. FPA008 Inhibition of CSF1R Signaling

[redacted]

1.2.2. Nonclinical Pharmacokinetics and Pharmacodynamics

1.2.2.1. Pharmacokinetics

[redacted]

1.2.2.2. Pharmacodynamics

[redacted]

1.2.3. Nonclinical Toxicology Studies and Findings

[redacted]

[redacted]

[redacted]

1.3. Clinical Experience with FPA008

This study was initiated in June 2015. Nine patients have been treated with FPA008 in the dose escalation portion of the study, three patients each at 1 mg/kg, 2 mg/kg, and 4 mg/kg respectively. All nine patients completed the DLT observation period. There were no DLTs observed during dose-escalation and the MTD was not reached. Based on an assessment of safety, tolerability, and PK, an RD of 4 mg/kg was selected to proceed to Phase 2.

The safety and preliminary efficacy of FPA008 is currently being evaluated in two additional clinical trials. Study FPA008-001 is a double-blind, randomized, placebo-controlled first-in-human trial designed in three parts to study safety, pharmacokinetics (PK), and PD biomarkers. In Part 1, eight healthy volunteers were randomized (3:1) to receive a single intravenous infusion of FPA008 or placebo, per dose cohort of 0.2, 1, 3, or 10 mg/kg. In Part 2, eight healthy volunteers were randomized (3:1) to receive two doses of FPA008 or placebo administered 14 days apart, at 1 mg/kg or 3 mg/kg. Dose escalation decisions were based on the incidence of dose limiting toxicities (DLTs) plus attributed adverse events beyond the DLT period. Part 3 consisted of an open-label evaluation of three dose levels in RA patients whose disease is not responding to disease modifying anti-rheumatic drugs (DMARDs) and on a stable dose of methotrexate. In the open-label part, three subjects per dose level received two doses of FPA008 at 1, 3, or 6 mg/kg administered intravenously 14 days apart. Three and six subjects received three doses at 3 mg/kg or 6 mg/kg respectively. Enrollment is completed for study FPA008-001; analysis and interpretation of the clinical data is pending.

FPA008 is also being tested as a monotherapy and in combination with nivolumab for patients with advanced cancers in the FPA008-003 study. This study is a Phase 1a and 1b, open-label, multicenter, dose escalation and dose expansion study. Phase 1a consists of two planned FPA008 monotherapy reference cohorts (2 mg/kg and 4 mg/kg) and three planned cohorts of FPA008 in combination with nivolumab (1 mg/kg, 2 mg/kg, and 4 mg/kg FPA008 with a fixed dose of nivolumab). Phase 1b consists of seven expansion cohorts across six cancer types, enrolling 30 patients per disease-specific cohort. This study is currently in dose escalation.

1.3.1. Clinical Safety Summary of FPA008

[redacted]

[redacted]

1.3.2. Clinical Pharmacology Summary of FPA008

[redacted]

[redacted]

[redacted]

1.3.3. Clinical Experience Involving Serum Enzyme Elevations

[redacted]

[redacted]

Table 1a: Effect of FPA008 on LFT Elevations in Clinical Study FPA008-001 Part 1

[redacted]

Table 1b: Effect of FPA008 on LFT Elevations in Clinical Study FPA008-001 Part 3

Type							

Table 1c: Effect of FPA008 on LFT Elevations in Clinical Study FPA008-002 and FPA008-003

[redacted]

1.4. Risk-Benefit Assessment

[redacted]

[redacted]

[redacted]

[redacted]

[redacted] hat [redacted]

2. Study Objectives and Endpoints

2.1. Primary Objective

- Phase 1: To determine the recommended dose (RD) of FPA008 in patients with PVNS/dt-TGCT
- Phase 2: To estimate the objective response rate (ORR = CR+PR) of FPA008 in patients with PVNS/dt-TGCT

2.2. Secondary Objectives

- To characterize the safety and tolerability of FPA008 in patients with PVNS/dt-TGCT
- To determine the duration of response in responding patients
- To assess the pharmacokinetics of FPA008 in patients with PVNS/dt-TGCT

2.3. Exploratory Objective

- [redacted]
- To evaluate synovial fluid for FPA008 concentration and changes in cellularity in selected patients
- To assess functional outcomes as measured by the Ogilvie-Harris score developed specifically for PVNS and by the Brief Pain Inventory, and the Joint Stiffness Numeric Rating Scale.

2.4. Primary Study Endpoints

- Phase 1: The incidence of Grade 3 and Grade 4 adverse events (AEs) and clinical laboratory abnormalities defined as dose-limiting toxicities (DLTs)
- Phase 2: The incidence of confirmed objective responses per RECIST 1.1

2.5. Secondary Endpoints

- PK parameters
- The incidence of AEs, clinical laboratory abnormalities, and ECG abnormalities
- Duration of response per RECIST 1.1

2.6. Exploratory Endpoints

- PD parameters
- Symptom and Functional Outcomes as measured by:
  - Ogilvie-Harris score developed specifically for PVNS
  - Brief Pain Inventory (short form)
  - Joint Stiffness Numeric Rating Scale

3. Overall Design and Plan of the Study

3.1. Overview

This is a Phase 1/2 study. Phase 1 is a dose escalation, open-label, safety, tolerability, PK, and PD study of FPA008. Patients will be enrolled into either Phase 1 or Phase 2 of the study, but not both.

Enrolled patients will be treated in 28-day cycles. Each cycle will consist of 2 doses: on Day 1 and Day 15.

3.1.1. Screening Period

All Screening evaluations must be completed and reviewed by the Investigator and Medical Monitor to confirm that patients meet all eligibility criteria before the first infusion of FPA008 (Appendix 1). Written informed consent for participation in the study must be obtained before performing any study specific Screening tests or procedures. Screening assessments will be performed within 28 days prior to the first dose of FPA008 unless otherwise specified.

Study-procedure-related AEs that occur after signing of the informed consent form and before administration of the first FPA008 dose will be collected during this period.

3.1.2. Phase 1 (Dose Escalation)

Dose escalation will continue until either the MTD or maximum feasible dose is reached, with a minimum of 3 patients enrolled in each cohort. The anticipated dose levels and schedules are:

- Dose level 1: 1 mg/kg q2w
- Dose level 2: 2 mg/kg q2w
- Dose level 3: 4 mg/kg q2w

All dose escalation decisions will be based on assessment of DLTs, overall safety, and tolerability and will be made after the last patient enrolled in each cohort has completed the first treatment cycle. Dose escalation decisions will be agreed upon between the Investigators and the Sponsor. Prior to initiating each new dose level or expanding an existing dose level, a safety teleconference will be held wherein Investigators and the Sponsor review patient data, including, but not limited to, demographics, FPA008 dosing, concomitant medications, hematology and serum chemistry, and AEs; and confer and document agreement that dose escalation or expanding an existing dose level is considered appropriate. If the Sponsor and Investigators collectively agree that following review of safety and pharmacokinetic data, that a different dose escalation scheme should be used than the one outlined, this will be permitted. Review of safety, PK and PD parameters may inform decisions to add cohorts with alternative dose levels or dose regimens (e.g., less frequent dosing or with a loading dose) in order to reach an optimal target exposure.

The following algorithm will be used for dose escalation decisions:

Table 2: Dose-Escalation Considerations

Number of Patients with DLT at a Given Dose Level	Dose Escalation Decision Rule
0/3	Escalation will occur to the next higher dose cohort
1/3	Enroll three more patients in same cohort
≥ 2/3	Stop enrollment. Enter three more patients at dose level below, if only three were previously entered
1/6	Open next cohort
≥ 2/6	Stop enrollment. Enter 3 more patients at a dose level below or at an intermediate dose level if the current dose level is ≥ 50% higher than the previous dose level

The MTD is defined as the highest dose associated with DLTs in less than 33% of patients receiving FPA008 administered on Days 1 and 15 of a 28-day cycle. This will normally be the dose recommended for further study (RD); however, based on review of safety and PK data, the RD could be lower than the MTD. If the MTD is not reached, and the highest evaluated FPA008 dose is well tolerated, the data will be reviewed to assess whether further dose escalations are warranted. The protocol may be amended if additional dose escalation is considered appropriate.

If the MTD is not reached during Phase 1, or subsequent cycles of treatment in Phase 1 provide additional insight on the safety profile, an RD may be selected based on overall tolerability, safety, and PK.

After declaring the RD, the Sponsor and Investigators may decide to evaluate alternative dose levels to those defined in the protocol if the safety, PK, PD, and efficacy data support further evaluation of additional doses in order to reach an optimal target exposure. The dose escalation rules outlined in Section 3.1.2 will apply to the additional cohorts.

If a patient does not receive 2 doses and does not complete the safety and PK assessment in Cycle 1 for reasons other than toxicity (e.g., disease progression or withdrawal of consent), then an additional patient will be enrolled into the cohort so that the cohort has at least three patients evaluable for tolerability through Cycle 1. All such discussions and decisions will be documented as part of the dose escalation decision-making process.

Intra-patient dose escalation above the starting dose for each patient is not permitted.

If a patient's dose is decreased for an adverse event, dose escalation to the originally assigned dose may occur after resolution of the AE and after discussion with and approval by the Sponsor. Recurrence of the AE to greater than Grade 2 will result in permanent dose reduction without the opportunity for re-escalation.

On completion of Cycle 1 (Safety and PK Assessment Period), Phase 1 patients may participate in an Extended Treatment Period, which begins on Day 1 of Cycle 2. FPA008 will be administered every 2 weeks in 4-week cycles for up to 24 weeks of treatment or until disease progression (if before 24 weeks of treatment), unacceptable toxicity, patient or physician decision to discontinue, death, or Sponsor termination of the study (as defined in Section 9.12), assuming no limitations with availability of drug supply, or other issues that may preclude the Sponsor from providing FPA008.

3.1.3. Phase 2

Enrollment in Phase 2 will begin when the RD has been identified by the CRC, based on overall safety, tolerability, objective response, PK, PD and estimates of efficacious exposures extrapolated from nonclinical data. If dose escalation continues higher than 4 mg/kg, the RD may or may not be an MTD, if an MTD is identified in Phase 1. For example, if an MTD is not reached, or if exposure at the MTD is much higher than the level believed to be required for efficacy, or if subsequent cycles of treatment provide additional insight on the safety profile, then the RD may be a different, though not higher, dose than the MTD.

After initiation of Phase 2, the RD may be changed based on data from continued dose exploration. Any change in the RD for Phase 2 will only apply to newly enrolled patients. There will be no intra-patient dose-escalation. The total number of patients for enrollment in Phase 2 will be approximately 25-30, irrespective of the assigned dose.

Treatment is planned to continue every 2 weeks for up to 24 weeks of treatment (no more than 12 doses) or until disease progression.

If a patient appears to have stable or improving symptoms with stable measurable disease or better by MRI, but is having intolerable or Grade 3 or greater adverse events, dose reduction by 25–50% may be allowed with Sponsor agreement.

3.1.4. Retreatment Cohort

At the discretion of the Sponsor, patients from the 1 mg/kg or 2 mg/kg cohorts may be retreated at the RD after a washout period of at least 4 months and rescreening.

Patients treated at lower dose levels (1 mg/kg and 2 mg/kg FPA008) during Phase 1 may be treated at the RD for an additional 6 cycles (12 doses). Some of the patients treated at 1 mg/kg and 2 mg/kg had symptomatic relief without any radiological response. Treating these patients at the RD will provide an expanded safety profile. This will also provide additional information on assessment of efficacy through both RECIST and Patient-Reported Outcomes (PROs) after the re-treatment.

The patients eligible for this cohort will have already met the primary eligibility requirements, completed 6 cycles of initial treatment at either the 1 mg/kg or the 2 mg/kg dose levels, and have completed the end-of-treatment follow-up period. Prior to re-treatment, potential patients will

need to provide written informed consent and be re-assessed to ensure they meet the same eligibility requirements as untreated (naïve) patients.

3.2. Procedures

Patients will undergo safety evaluations (DLTs and other AEs, vital signs, ECGs, clinical laboratory tests), determination of ECOG performance status (PS), and physical examinations (Appendix 1). Additionally, blood samples will be collected for PK and PD analyses for all patients (Appendix 2).

MRI of affected joints will be performed at Screening, 4, 8, and 16 weeks following the start of treatment. An MRI should also be performed at the 30 days (±7 days) and 90 days (±7 days) End of Treatment Follow-up Visits unless already performed within the previous 6 weeks or if tumor progression was previously determined. Patients who have not progressed and enter Long-Term Follow-up should have MRI every 14 (± 2) weeks until progression, the patient undergoes local therapy (e.g., resection, radiation) or a new systemic therapy is initiated, for up to 52 weeks following C1D1. Response per MRI will be assessed using RECIST 1.1 and TVS based on independent central radiology review.

Clinical assessment of health outcomes (function, symptoms) will be done at baseline, Cycle 1 Day 15, Cycle 2, Day 1 and then approximately every 4 weeks, prior to the administration of study drug.

Safety will be assessed by monitoring AEs and changes in physical examinations, weight, vital signs, 12-lead ECGs, and laboratory measurements. Assessment of AEs will follow the guidelines provided in the National Cancer Institute (NCI) – Common Terminology Criteria for Adverse Events (CTCAE), version 4.03. Blood samples will also be drawn at scheduled time points (Appendix 2) during the study for determination of drug serum concentration, and anti-drug antibodies (ADAs) (i.e., antibody response to FPA008).

In patients who have archival tumor tissue available and who have signed the Optional Research Sample Informed Consent Form, the tissue will be evaluated for *CSF1* gene translocation if not previously done (Appendix 1). In addition, CSF1 and CSF1R and CD68 markers and will be determined.

For patients who sign the applicable Optional Research Sample Informed Consent Form, baseline tumor tissue resections (≥0.5 cm to ≤2 cm) and synovial fluid (if applicable) will be obtained from patients prior to starting FPA008 treatment and after eligibility criteria have been fulfilled. The baseline tissue sample will be reviewed by a pathologist to determine whether the tissue is evaluable. If the Screening tissue sample is evaluable, a subsequent biopsy will be performed before the Cycle 2, Day 1 administration of FPA008 (Appendix 1).

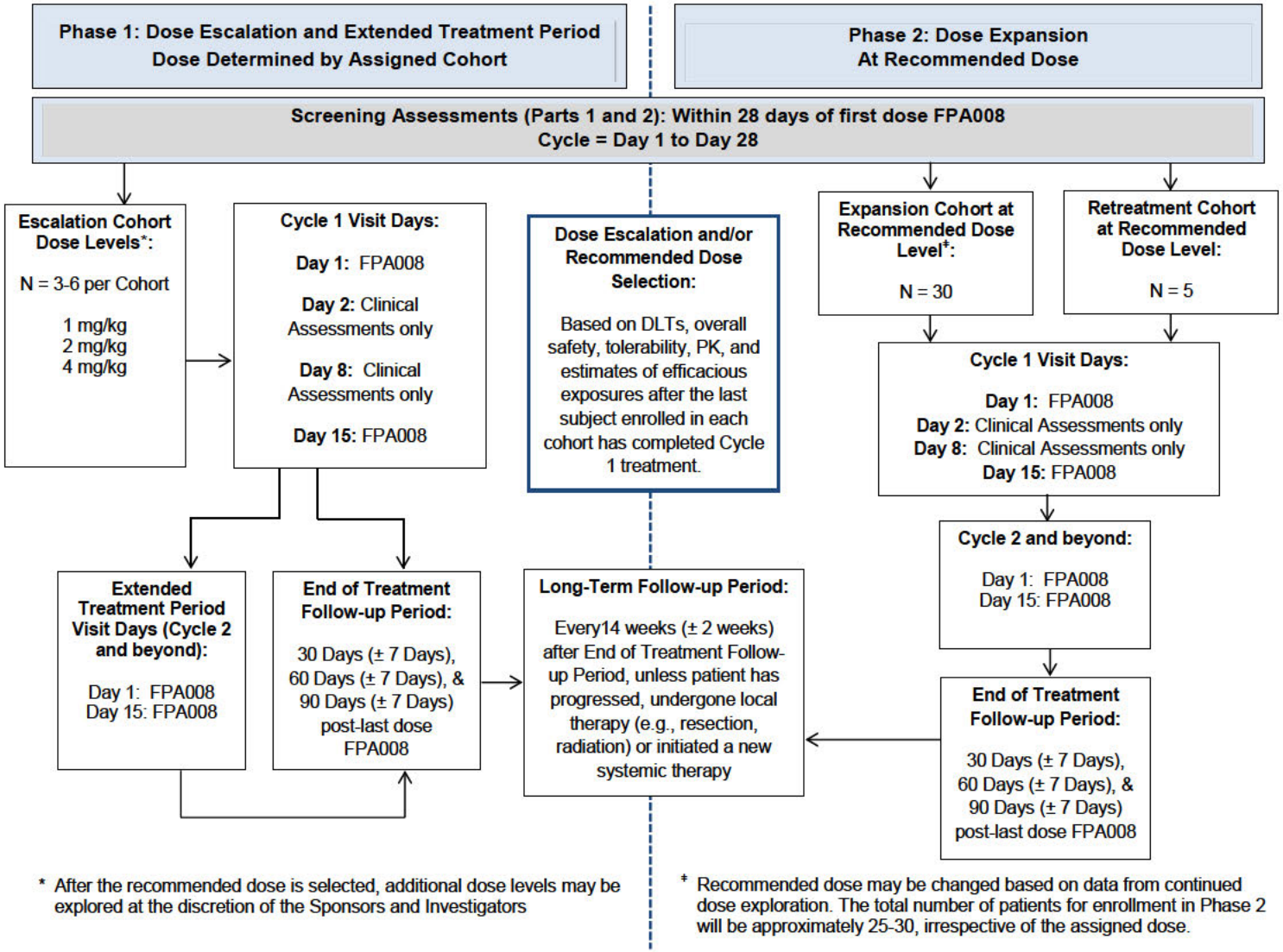
Patients enrolled in Phase 1 or Phase 2 of the study may continue treatment with FPA008 in 28-day cycles for up to 24 weeks of treatment or until disease progression, intolerable toxicity, patient or physician decision to discontinue, or Sponsor termination of the study. Responding

patients who discontinue treatment while still in response (CR, PR or SD) should get follow-up scans at 14 (±2)-week intervals during the Long-Term Follow-up Period to determine the duration of response, unless other therapy is started for the treatment of PVNS/dt-TGCT or consent is withdrawn.

Approximately ten patients enrolled in Phase 2 will undergo a PET scan at Screening, Cycle 3 Day 1 (±7 days), Cycle 6 Day 15 (±7 days) Visit, 90 days (±7 days) End of Treatment Follow-pp Visit, and at the first Long-Term Follow-up Visit (14 weeks (± 2 weeks) post 90 days End of Treatment Visit).. All patients should return to the clinic for three End of Treatment Follow-up visits irrespective of whether a patient is withdrawn or withdraws at a planned visit or mid-cycle.

AEs will be assessed from the time the first dose of FPA008 is administered through 90 days (±7 days) after the last dose of FPA008 (see Section 6.2.1.1). All serious adverse events (SAEs) will be collected after signing of the informed consent form through 90 days (±7 days) after the last dose (see Section 6.2.1.1).

3.3. Study Schema



3.4. Rationale for the Study Design

The Phase 1 component of this study is a dose escalation, open-label study to assess the safety, PK, PD, and preliminary efficacy of FPA008 in patients with PVNS/dt-TGCT. The 3+3 dose escalation design is standard for early stage trials of novel anticancer treatments.

The Phase 2 component is a single-stage trial designed to estimate the objective response rate with a precision of approximately 20%, assuming the response rate is similar to that reported for PLX3397 and RG.7155, other potent inhibitors of the CSF1R signaling pathway. The Phase 2 component will also allow a more thorough investigation of the safety, PK, and biological effects of FPA008 in the target population for future trials.

3.4.1. Rationale for Modification of DLT Criteria

4. Study Eligibility and Withdrawal Criteria

4.1. Planned Number of Patients and Study Centers

Phase 1: Approximately 12-15 patients with PVNS/dt-TGCT will be enrolled. Enrollment in Phase 1 will continue until the MTD has been reached or until the RD for Phase 2 has been defined.

Phase 2: Approximately 25-30 patients with PVNS/dt-TGCT will be enrolled.

Retreatment Cohort: Up to 5 patients from the 1 mg/kg and 2 mg/kg cohorts from Phase 1 who completed 6 cycles of treatment may be enrolled at the Sponsor's discretion.

The study will be conducted at approximately 11 investigational centers in North America, Europe, and Asia.

4.2. Inclusion Criteria for Study Participation

Patients enrolling into Phase 1 or 2 must meet ***all*** of the following inclusion criteria:

1. Understand and sign an Institutional Review Board/Independent Ethics Committee-approved informed consent form prior to any study-specific evaluation
2. Age ≥18 years
3. Histologically confirmed diagnosis of inoperable PVNS/dt-TGCT or potentially resectable tumor that would result in unacceptable functional loss or morbidity as determined by a qualified surgeon or multi-disciplinary tumor board (must be documented in the CRF during screening)
4. Measurable PVNS/dt-TGCT by RECIST 1.1 on MRI
5. ECOG performance status ≤1
6. Willing and able to comply with all study procedures
7. In sexually-active patients (i.e., females of childbearing potential, who have not undergone menopause as defined by 12 consecutive months of amenorrhea or had a permanent sterilization procedure and males, who have not had a permanent sterilization procedure), willingness to use 2 effective methods of contraception, of which one must be a physical barrier method (condom, diaphragm, or cervical/vault cap) until 6 months after the last dose of FPA008. Other effective forms of contraception are permanent sterilization (hysterectomy and/or bilateral oophorectomy, or bilateral tubal ligation with surgery, or vasectomy) at least 6 months prior to Screening. Females <55 years of age should have FSH >40. Female patients of childbearing potential must be on stable oral contraceptive therapy or intrauterine or implant device for at least 90 days prior to the study, or abstain from sexual intercourse as a way of living.

4.2.1. Retreatment Cohort

Patients enrolling in this portion of the study must also meet the following inclusion criterion:

8. Completed six cycles of initial treatment at the 1 mg/kg or 2 mg/kg dose levels and the End of Treatment Follow-up Period.

   ***Note*:** Prior to re-treatment, potential patients in this cohort will be re-assessed to ensure they meet the same eligibility requirements as untreated patients.

No waivers of these inclusion criteria will be permitted.

4.3. Exclusion Criteria for Study Participation

Patients enrolling into Phase 1 or 2 will be excluded if any of the following criteria apply:

1. Prior therapy with an anti-CSF1R antibody (with the exception of patients previously treated with FPA008 who will be enrolled in the Retreatment Cohort)
2. Prior therapy with PLX3397 unless discontinued for intolerance (i.e., non-progression on prior kinase inhibitor); prior therapy with imatinib or nilotinib is allowed
3. CK and liver function tests (including ALT, AST, and total bilirubin), outside of the range of local laboratory normal at Screening
4. Inadequate organ or bone marrow function defined as: hemoglobin < 10 g/dL, absolute neutrophil count <1.5x 10^9/L, platelet count <100x 10^9/L, serum creatinine >1.5x ULN or calculated creatinine clearance <30 mL/min
5. Any surgical procedure of the involved joint within 12 weeks prior to first study dose administration (except baseline synovium biopsy, if performed)
6. Current or history of clinically significant muscle disorders (e.g., myositis), recent unresolved muscle injury, or any condition known to elevate serum CK levels
7. History of congestive heart failure or myocardial infarction <1 year prior to first study dose administration
8. Decreased cardiac function with NYHA > Class 2
9. Uncontrolled or significant heart disorder such as unstable angina
10. Significant abnormalities on ECG at Screening. QTcF >450 msec for males or >470 msec for females at Screening
11. Contraindications to MRI and use of intravenous gadolinium-based contrast agents
12. History of severe allergic, anaphylactic, or other infusion related reaction to a previous biologic agent
13. Treatment with any anticancer therapy or participation in another therapeutic clinical study with investigational drugs ≤ 28 days prior to first dose of FPA008

14. Known history of ADAs to previous biologic agents
15. Known history of sensitivity to Tween 20 (polysorbate 20)
16. Consumption of non-pasteurized milk on a regular basis, or known significant risk of exposure to opportunistic intracellular infections such as *listeria,* or other such pathogens.
17. Receipt of any vaccine within 28 days prior to first day of treatment. The effect of FPA008 on mounting an immunologic vaccine response is not known. Flu or other vaccinations may be administered while on study but the impact of FPA008 on the safety and efficacy of the vaccination is unknown.
18. Current unresolved infection or history of chronic active clinically significant infection (viral [e.g., HBV, HCV], bacterial, fungal, or other), which in the opinion of the Investigator would place the patient at risk from exposure to a CSF1R inhibitor
19. Known positive test for human immunodeficiency virus (HIV)
20. Active TB
21. Positive test for latent TB at Screening (Quantiferon test)
22. History of prior malignancy, except:
    - Curatively treated non-melanoma skin malignancy
    - Cervical cancer in situ
    - Solid tumor treated curatively more than 2 years previously without evidence of recurrence
23. Lack of peripheral venous access or any condition that would interfere with drug administration or collection of study samples
24. Any uncontrolled medical condition or psychiatric disorder which in the opinion of the Investigator would pose a risk to patient safety or interfere with study participation or interpretation of individual patient results
25. Inability to perform and/or comply with study and follow-up procedures
26. Known history of metastatic PVNS/dt-TGCT

No waivers of these exclusion criteria will be permitted.

4.4. Patient Withdrawal and Replacement

The patient has the right to stop treatment or to withdraw from the study at any time. Patients may continue to repeat cycles (up to 6 cycles) of FPA008 treatment until at least one of the following criteria applies:

- Consent withdrawal at the patient's request or at the request of their legally authorized representative

- Progression of patient's underlying disease
- Any event that would pose an unacceptable safety risk to the patient
- An intercurrent illness that would affect assessments of the clinical status to a significant degree and require discontinuation of therapy
- A positive pregnancy test at any time during the study
- At the specific request of the Sponsor or its authorized representative (for example, if the study is terminated for reasons of patient safety)

The date and reason for cessation of FPA008 will be documented, and the Investigator must make every effort to perform the End of Treatment Follow-Up visits. Patients will be followed for 90 days (±7 days) after the last dose of FPA008 for safety. Those with ongoing SAEs will be followed until either resolution or stabilization.

Data from patients who discontinue prematurely will remain part of the study database.

4.5. Patient Identification and Enrollment

Patients must be able to provide written informed consent and meet all inclusion criteria and none of the exclusion criteria. No waivers of inclusion or exclusion criteria will be granted by the Investigator and Sponsor or its designee for any patient enrolled in the study. Before enrolling a patient, all eligibility criteria must be satisfied. Patients who qualify for Phase 1 of the study will be enrolled into the first available cohort. In Phase 2, a cohort of approximately 25-30 patients will be enrolled. At the Sponsor's discretion, up to 5 patients from the 1 mg/kg or 2 mg/kg cohorts may be retreated at the RD in the Retreatment Cohort. A total of approximately 42-45 patients will be enrolled in the study.

The Investigator may repeat qualifying lab tests and vitals/ECGs prior to enrollment if a non-qualifying finding is considered an error or an acute finding is likely to meet eligibility criteria on repeat testing.

5. Study Drug

5.1. FPA008 Drug Product

The investigational drug product in this study is FPA008. The investigational supply of FPA008 will be provided to the study centers by the Sponsor (or designee) and will be administered to patients in the clinical study by a trained healthcare professional.

A brief description of the FPA008 drug product is provided below:

- [redacted]

5.2. Administration

The dose of FPA008 will be administered based on weight to patients in this study.

[redacted] FPA008 will be administered under medical supervision over approximately 30-minute (± 5 minutes) IV infusion via a peripheral vein or central venous catheter.

If a patient experiences an infusion reaction prior to completion of the infusion, the infusion must be stopped, and the patient should be promptly managed according to signs and symptoms, and local clinical protocol. The infusion may be restarted at a slower rate if all signs and symptoms have resolved. If the signs and symptoms do not resolve, the infusion should not be restarted. Patient should be kept under close observation for at least 1 hour after the end of study drug infusion.

All vials are for single use only. Instructions on study drug preparation and administration will be provided in the Pharmacy Manual.

5.3. Starting Dose and Dose Modifications

The starting dose level of FPA008 and subsequent dose escalations between cohorts in Phase 1 are described in Section 3.1.2. The dose of FPA008 in Phase 2 will be determined by evaluation of the data from Phase 1 of the study.

5.3.1. Dose Escalation of FPA008 between Cohorts

Dose escalation to the next cohort will only start after the preceding dose cohort has completed the DLT period. Twenty-eight days (DLT period) of safety data must be available for at least 3 safety-evaluable patients prior to a potential dose-escalation decision by the CRC per the CRC Charter. In the event that a patient in a cohort is lacking adequate safety data (e.g., due to early withdrawal from study or poor compliance with the protocol), an additional patient will be enrolled to the cohort.

Dose escalation in each successive dose cohort will proceed in a stepwise fashion. All relevant safety information for the first cohort or the preceding dose cohort will be reviewed by the CRC (see Section 9.10).

Dose escalation is planned to continue until dose-limiting toxicities occur in 2 or more patients in a cohort. The decision to discontinue dose escalation will be made jointly by the Sponsor and Investigator(s) based on reaching the MTD or a dose level that shows an adequate pharmacodynamic effect.

In Cohort 1, three patients will be enrolled initially at a starting dose of 1 mg/kg FPA008, given by infusion. The occurrence of DLTs (Section 5.3.3) will determine whether the dose will be escalated in subsequent cohorts.

The dose escalation decision rules are summarized in Table 3.

Table 3: Decision Criteria for Escalation

Number of Patients with DLTs	Action
0/3	Open next cohort
1/3	Enroll 3 more in same cohort
≥ 2/3	Stop enrollment. Enter 3 more patients at dose level below, if only 3 were previously entered
1/6	Open next cohort
≥ 2/6	Stop enrollment. Enter 3 more patients at a dose level below or at an intermediate dose level if the current dose level is ≥ 50% higher than the previous dose level

5.3.1.1. Maximum Tolerated Dose

The selection of the RD will be based on clinical response data as well as PK and PD profiles. The Sponsor and Investigators may decide to discontinue dose escalation before reaching the highest planned dose of 4 mg/kg or, potentially, evaluate a higher (>4 mg/kg) dose if the safety, PK, and PD data support evaluation of different dose levels.

Escalation to an MTD is not intended, however, may occur. If so, the MTD is defined as the highest dose associated with DLTs in Cycle 1 in less than 33% of patients receiving FPA008 administered on Day 1 and Day 15 of a planned 28-day cycle.

If the MTD is not reached during Phase 1 or subsequent cycles of treatment in Phase 1 provide additional insight regarding the safety profile, the RD may be selected depending on overall tolerability, PK, and estimates of efficacious exposures extrapolated from ongoing clinical evaluations.

After declaring the RD, the Sponsor and Investigators may decide to evaluate alternative dose levels than those defined in the protocol if the safety, PK, PD, and efficacy data support evaluation of additional doses in order to reach an optimal target exposure. The same dose escalation rules specified in Section 3.1.2 will apply to the additional cohorts.

5.3.1.2. Toxicity at Lowest Dose Level

If the first dose level of 1 mg/kg is, unexpectedly, found to exceed an MTD, then decisions on how to proceed will be based on safety, tolerability, and PK data; and will be agreed on between the Investigators and the Sponsor.

A lower dose level may be chosen as the next cohort.

5.3.2. Dose Escalation within a Cohort

Intra-patient dose escalation above the starting dose is not permitted. If a patient's dose is decreased for an AE, dose escalation to the originally assigned dose may occur after resolution of the AE and after discussion with and approval by the Sponsor. Recurrence of the AE to greater than Grade 2 will result in permanent dose reduction without re-escalation.

5.3.3. Dose-Limiting Toxicity

DLTs are defined as any Grade ≥3 related adverse event that occur during Cycle 1 of treatment and are assessed by the Investigator with concurrence by the CRC as related to FPA008 with the following exceptions:

- In the absence of clinical symptoms and other accompanying changes in bilirubin, serum elevations of AST and/or ALT ≤ 12 X ULN will not be considered a DLT and serum elevations of CK and/or LDH ≤ 15 X ULN will not be considered a DLT.

- In the absence of clinical symptoms and other accompanying changes in bilirubin, serum elevations of AST and/or ALT > 12x ULN and ≤ 20x ULN that last for ≤ 7 days will not be considered a DLT and serum elevations of CK and/or LDH > 15x ULN and ≤ 20x ULN that last for ≤ 7 days will not be considered a DLT.

As applicable, events will be classified according to the NCI CTCAE (Version 4.03).

Phase 1 patients who experience a DLT during the DLT assessment period (Cycle 1) will be removed from study treatment. Patients experiencing toxicity in cycles after Cycle 1 that would be considered dose limiting during the DLT assessment period are not required to discontinue study participation in the study.

5.3.4. Dose Modification Criteria

Dose reductions may be permitted for patients on prolonged treatment beyond the DLT period in Phase 1 or any patient in Phase 2 per the following guidelines. If dose reductions or interruptions that do not fall within these guidelines are being considered by the Investigator, these will require discussion with and approval by the Sponsor.

Patients may miss up to 2 consecutive doses (up to 6 weeks between doses) for adverse or other events and may resume the study drug if the event returns to baseline or ≤ Grade 1 within 6 weeks of treatment interruption. Omission of additional dosing longer than 6 weeks for adverse events will necessitate the patient's discontinuation from the study unless allowed by the Sponsor. Patients may miss doses in the course of participation in the study, including missed doses for scheduled vacations or other personal reasons as needed, but not more than 2 doses sequentially.

The Cycle 2, Day 1 infusion of FPA008 can only be administered after completion of the 28-day DLT window. All subsequent infusions can be administered with a ±3 day window. Patients should not have 2 doses of FPA008 within 7 days. The first dose of each cycle is considered Day 1 of each cycle, cycles will repeat every 28 days unless there is a treatment delay. Patients can have treatment delay of Day 1 of the subsequent cycle as long as the Day 1 treatment is within 6 weeks of the last treatment.

Dose modification guidelines in the event of ALT, AST, CK and LDH elevations are summarized in Table 4:

Table 4: Dose Delay and Modification Guidelines for ALT, AST CK and LDH Elevations

Serum Elevation	Management	Follow-Up
AST or ALT > 3.0x ULN ***and*** Total bilirubin > 2x ULN **or** INR > 1.5	– Discontinue FPA008 therapy	– Continue LFT monitoring until resolution. – Continue monitoring for and other associated clinical signs or symptoms – Contact the Medical Monitor – Evaluate for non-drug related causes of the laboratory abnormalities (e.g. obstruction, viral infection, Gilbert's disease, etc.) – Under selected circumstances (e.g. alternative etiology is identified), patient may receive additional therapy only after consultation and agreement between the Sponsor/MM and the investigator if receiving additional treatment with FPA008 is in the best interest of the patient (e.g. if the subject has demonstrated a response to therapy)
AST or ALT > 5 to ≤ 12x ULN ***and*** Total bilirubin ≤ 2x ULN	– Continue FPA008 therapy if there are no clinical signs of significant muscle or hepatic damage – Increase frequency of monitoring of AST, ALT, bilirubin, alkaline phosphatase and INR (every 48-72 hours or more frequently, as clinically indicated) – Monitor for other clinical symptoms (fatigue, nausea, vomiting, abdominal pain, fever, rash, and/or eosinophilia)	– Contact the Medical Monitor if there are clinical signs of muscle or hepatic injury or other clinical symptoms – Contact the Medical Monitor if there is a concurrent increase of bilirubin, AST, ALT, or alkaline phosphatase from baseline. – Notify the Medical Monitor if there is an AST increase > 5x ULN – Frequency of retesting can decrease to once a week or less if abnormalities stabilize or the trial drug has been discontinued and the subject is asymptomatic – Consider gastroenterology or hepatology referral
AST or ALT > 12 to ≤ 20x ULN ***and*** Total bilirubin ≤ 2x ULN ***or*** Isolated total bilirubin > 2 to ≤ 3x ULN	– Delay FPA008 therapy – Increase frequency of monitoring (including but not limited to) of AST, ALT, bilirubin, alkaline phosphatase and INR (every 48-72 hours or more frequently, as clinically indicated) – Monitor for other clinical symptoms (fatigue, nausea, vomiting, abdominal pain, fever, rash, and/or eosinophilia) – Consider imaging to rule out obstruction	**If AST and ALT ≤ 12x ULN for ≤ 7 days:** – Resume routine monitoring – Resume FPA008 therapy at same dose level **If elevations persist and remain at same level for > 7 days but < 28 days:** – Discontinue further dosing – Continue monitoring subject and consider dosing the subject with FPA008 at the same dose or one dose level lower upon resolution to Grade 1 or baseline after discussion with the medical monitor. **If elevations persist at same level for > 28 days or worsen:** – Discontinue FPA008 therapy – Discuss with Medical Monitor
AST or ALT > 20x ULN ***or*** Total bilirubin > 3x ULN	– Discontinue FPA008 therapy	– Continue LFT monitoring until resolution – Continue monitoring for and other associated clinical signs or symptoms
CK > 10x ULN	– Consider measuring CK isoenzymes as clinically indicated	**If CK isoenzymes are abnormal** – Consider checking troponin levels – Consider other assessments (including uromyoglobin) as clinically indicated **If CK isoenzymes are normal** – Continue dosing, per protocol **Monitor CK level as clinically indicated**

Serum Elevation	Management	Follow-Up
CK or LDH > 15 to ≤ 20x ULN	– Delay FPA008 therapy – Measure CK isoenzyme panel to identify source of elevation – Increase frequency of monitoring (every 48-72 hours, or more, as clinically indicated) – Notify the Medical Monitor	**If returns to ≤ 15x ULN within ≤ 7 days:** – Resume routine monitoring, resume FPA008 therapy at same dose level – If CK isoenzyme panel is normal continue monitoring the subject. – If CK isoenzyme panel is abnormal then consider measuring troponins. – If troponins are abnormal, contact Medical Monitor to determine if the subject can be retreated. **If elevations persist and remain at same level > 7 days but < 28 days:** – Discontinue further dosing – Continue monitoring and consider dosing the subject with FPA008 therapy at the same dose or one dose level lower upon resolution to Grade 1 or baseline after discussion with the medical monitor. **If elevations persist at the same level > 28 days or worsen:** – Discontinue further dosing – Discuss with Medical Monitor
CK or LDH > 20x ULN	– Discontinue FPA008 therapy	– Follow up until resolution

Table 5: Dose Delay and Modification Guidelines for Study Drug-Related Events other than ALT, AST CK and LDH Elevations

Toxicity Grade	FPA008 Dose	Dose Schedule
1	Continue 100% of dose	No delay or missed dose required
2	Continue 100% of dose	No delay or missed dose required
3	**Phase 1**: May continue at next lower dose level evaluated (e.g., if a Grade 3 AE occurs at 2 mg/kg, patient may continue at 1 mg/kg) following recovery to baseline or Grade 1; If at lowest dose level evaluated (i.e., 1 mg/kg), use Phase 2 dose modification guideline **Phase 2**: Continue 75% of starting dose following recovery to baseline or Grade 1	Up to 2 missed doses allowed without Sponsor approval to continue
4	**Phase 1:** May continue at next lower dose level evaluated (e.g., if a Grade 3 AE occurs at 2 mg/kg, patient may continue at 1 mg/kg) following recovery to baseline or Grade 1; If at lowest dose level evaluated use Phase 2 **Phase 2:** Continue 50–75% of starting dose following recovery to baseline or Grade 1	Up to 2 missed doses allowed without Sponsor approval to continue

Note: Table 5 applies to adverse events other than the ALT, AST, CK and LDH rules outlined in Table 4.

If a patient's dose is decreased for an adverse event, dose escalation to the originally assigned dose may occur after resolution of the AE and after discussion with and approval by the Sponsor. Recurrence of the AE to greater than Grade 2 will result in permanent dose reduction without re-escalation.

5.3.5. Dose Interruptions during Study Drug Infusion

Infusion of FPA008 must be stopped if any AE ≥ Grade 3 occurs during the infusion. If bronchospasm or dyspnea occurs in a patient during infusion, the infusion should be stopped.

In addition, at the Investigator's discretion, the infusion rate may be reduced or stopped if a less severe AE (Grade 1 or 2) occurs during the infusion. If a Grade 3 or less severe AE resolves within 6 hours, the infusion may be restarted at half the previous rate. If the same AE appears again with the same severity at any time during the restarted infusion, the infusion should be discontinued, and no further dosing of study drug will occur without consultation with the Sponsor (or designee).

If a patient experiences an infusion reaction, the patient's vital signs (temperature, blood pressure, pulse, and respiration rate) should be monitored during the infusion, as well as every 30 minutes after the infusion for a minimum of 1 hour and until resolution of the infusion reaction.

Systemic hypersensitivity reactions should be managed under the direct supervision of a physician and according to treatment protocols in effect at the investigational site. However, in the absence of such a protocol, the standardized treatment protocol provided in Appendix 7 should be used.

5.4. Blinding and Breaking the Blind

Blinding and breaking the blind are not applicable as this is an open-label study.

5.5. Drug Accountability

The Investigator or appropriately qualified staff is responsible for maintaining accurate study drug accountability records throughout the study.

The Investigator is responsible for returning all unused study drug to the Sponsor (or designee), and must verify that no remaining supplies are in the Investigator's possession. The study site is permitted to destroy used or partially used study drug vials according to the site policy once Sponsor (or designee) approval of its documented destruction procedure has been obtained. Accurate records of all study drug received at, dispensed from, returned to, and disposed of by the study site should be reconciled and recorded by using a drug inventory log during and on completion of the study.

5.6. Investigational Product Compliance

Only qualified trained site personnel may administer FPA008. Pharmacy personnel trained in the study requirements will monitor compliance with the treatment assignments. FPA008 will be infused over approximately 30 minutes via a peripheral vein or central venous catheter by a trained healthcare professional. Records of study medication administered (date, start and stop

time, and dose administered relative to time of preparation) will be recorded on the patient's electronic case report form (eCRF).

5.7. Concomitant Medication and Treatment

All concomitant medications including herbal and other non-traditional remedies are to be captured on the eCRF. The following parameters will be collected: generic name, route of administration, start date, stop date, dosage, frequency, and indication. Any changes in the dosage or regimen of a concomitant medication also must be recorded on the eCRF.

At Screening, patients will be asked what medications they have taken during the previous 28 days. At each subsequent study visit, patients will be asked about any changes in concomitant medications since the previous visit.

Throughout the study, Investigators may prescribe any concomitant medications or treatments deemed necessary to provide adequate supportive care ***except*** for the following:

- Other experimental drugs or devices
- Other systemic medication for treatment of PVNS such as imatinib or nilotinib
- Chronic daily corticosteroids ≥10 mg/kg prednisone (or equivalent)

If a patient uses a prohibited medication or undergoes tumor resection, the Sponsor should be consulted for a decision on whether the patient should be withdrawn from the study (see Section 9.12).

Patients may initiate or continue pain medications as dictated by standard clinical practice. Transfusions are permitted as needed.

No routine premedication will be administered for the initial FPA008 dose. If a patient develops nausea, vomiting, or other infusion-related AEs, the patient may be pre-medicated with antiemetics, steroids, or antihistamines prior to subsequent infusions of FPA008 at the discretion of the Investigator. The treatment will be administered according to the institution's standard practice, and should be captured on the patient's eCRF.

6. Parameters and Methods of Assessment

Safety of FPA008 will be assessed by monitoring AEs and changes in physical examinations (including weight), vital signs, 12-lead ECGs, disease related signs and symptoms, and clinical laboratory measurements. Blood samples will be evaluated for immunogenicity.

6.1. Tumor Response Parameters

MRI will be performed at Screening (within 28 days prior to first dose), 4, 8, and 16 weeks following the start of treatment (Appendix 1). MRIs should be completed within 1 week of dose administration when re-imaging is scheduled. All patients should have tumor response parameters assessed at the 30 days (± 7 days) and 90 days (± 7 days) End of Treatment Follow-up Visits, unless a tumor assessment has been performed within the previous 6 weeks or if tumor progression was previously determined.

Patients who have not progressed after the End of Treatment Follow-up Period are to be followed every 14 weeks (± 2 weeks) (see Section 7.2.10) until progression, the patient undergoes local therapy (e.g., resection, radiation) or a new systemic therapy is initiated, for up to 52 weeks following C1D1.

Response will be evaluated using RECIST 1.1 (Eisenhauer 2009) and the Total Volume Score (Tap 2014) for radiologically measurable disease. MRI will be used for radiologic measurement of tumor.

Linear measurements of diffuse PVNS are complicated by a number of factors. Since the tumors are characteristically amorphous and can fluctuate in shape, correlation of serial linear measurements with changes in tumor volume depends on where the measurements are made. However, poor contrast between the tumor and adjacent tissue in certain locations limits where these measurements can be made accurately. Additionally, linear measurements are highly vulnerable to variations in the plane of section on serially acquired images. Nevertheless, given the longstanding tradition of RECIST in oncology clinical trials, linear measurements of up to two measurable tumor locations per joint or tendon sheath, as per RECIST 1.1 guidelines, will be used in this study as a reference.

Radiologic response will also be assessed by the TVS. The TVS has been used in a recent study of PVNS that showed a treatment effect of a CSF1R tyrosine kinase inhibitor.

The clinical impact of PVNS is believed to stem primarily from the mass effect and local structural damage caused by tumor growth within limited articular and peri-articular spaces. Tumor growth interferes with joint flexion and can also destroy the structural and functional integrity of joints as tumor invades local bones and soft tissues. The goals of imaging in clinical trials of PVNS are thus to monitor changes in the volume of the tumor and to monitor any associated damage to local tissues.

Volumetric quantification of diffuse PVNS is complicated by irregular shape of the tumor, heterogeneous contrast between the tumor and its surrounding structures, and variable enhancement by intravenous gadolinium-based contrast agents. Tumor margins are thus difficult to delineate in certain locations, making automated segmentation unreliable and manual segmentation subjective. Hemosiderin deposition usually does not improve contrast substantially, as the distribution of hemosiderin is variable, heterogeneous, and not always confined to the tumor. Additionally, discriminating viable tumor from inactive scar tissue or intra- and peri-lesional fluid collections can be difficult. Under such circumstances, visual scoring using semi-quantitative ordinal scales is usually more reliable than volumetric quantification, as has been the experience with synovial thickening assessments in clinical trials of arthritis. Trials employing MRI for evaluation of anti-inflammatory therapy for arthritis have been based on semi-quantitative scoring.

The TVS scale is based on 10% increments of the estimated volume of the maximally distended synovial cavity, which varies from joint to joint, or of the maximally distended tendon sheath (assumed to be three times the diameter of the involved tendon). Thus, a tumor that is equal to the volume of a maximally distended synovial cavity or tendon sheath would be scored 10, whereas a tumor that was 70% of that volume would be scored 7, and a tumor twice that volume would be scored 20.

Individual patient outcomes by TVS are classified according to the following criteria:

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

***Note*:** Tumor assessments performed as part of the patient's standard of care within 28 days (4 weeks) of the first dose of FPA008 do not need to be repeated during Screening.

Approximately ten patients in Phase 2 will also undergo a PET scan at Screening, Cycle 3 Day 1 (±7 days), C6D15 (±7 days) Visit, 90 days (±7 days) End of Treatment Follow-up Visit, and at the first Long-Term Follow-up Visit (14 weeks (± 2 weeks) post 90 days End of Treatment Visit). PET scans will be locally read and interpreted according to RECIST guidelines, observing change in normalized standardized uptake value (SUV) for lesions in the affected joints (Eisenhauer 2009).

6.2. Safety Parameters

6.2.1. Adverse Events

6.2.1.1. Collection of Adverse Events

Any new symptoms, injury or worsening of symptoms that occur following signing of the informed consent form (ICF) but prior to first infusion (Cycle 1, Day 1) will be considered pretreatment events and reported on the Medical History page of the eCRF, unless they directly correlate to a study-related procedure. Adverse event reporting will continue through the End of Treatment Follow-up Period or until 90 days (±7 days) after the last dose of study drug. Serious AEs occurring after the end of the study should be reported to the Sponsor by the Investigator if the Investigator considers a causal relationship with the study drug.

Serious AEs should always be recorded on the AE eCRF page and the SAE form.

SAEs and new AEs will be collected until 90 days (±7 days) after the last dose of FPA008 (or withdrawal of consent). If an SAE comes to the attention of the Investigator after the final visit, information regarding the SAE should be collected and reported only if assessed to be related to study drug by the Investigator.

6.2.1.2. Definitions

An AE is any untoward medical occurrence that occurs in a patient administered a pharmaceutical product, and which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational product, whether or not considered related to the product.

All AEs including intercurrent illnesses that occur during the study, from the time of study drug administration, will be documented on the eCRF. Concomitant illnesses, which existed prior to the day of the first study infusion, will not be considered AEs unless they worsen by at least 1 grade during the treatment period. Intensity (severity) grade will be defined according to the NCI-CTCAE, version 4.03. Pre-existing conditions will be recorded on the Medical History eCRF.

A treatment-emergent AE will be defined as an AE that begins or worsens in severity after at least 1 dose of study drug has been administered.

Diagnostic and therapeutic non-invasive and invasive procedures, such as surgery, will not be reported as an AE, but the procedure and/or therapeutic treatment should be recorded on the appropriate eCRF. The medical condition for which the procedure was performed must be reported as an AE (or as part of the patient's medical history, if appropriate). Disease progression is an endpoint and therefore should not be reported as an AE or SAE.

6.2.1.3. Assessment of Adverse Events

Each AE will be assessed by the Investigator with regard to the following categories:

6.2.1.3.1. Seriousness

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

- Results in death. Death may occur as a result of the underlying disease process. All events other than progression of underlying disease that result in death during the reporting period up to 90 days (±7 days) following the last dose of FPA008 must be treated as an SAE and reported as such.
- Is life-threatening (patient is at immediate risk of death from the event as it occurred)
- Requires inpatient hospitalization (formal admission to a hospital for medical reasons) or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity
- Is a congenital anomaly or birth defect

Important medical events that may not result in death, are not life-threatening, or do not 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 are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

Medical and scientific judgment should be exercised in deciding whether a case is serious and whether expedited reporting is appropriate.

Hospitalization for an event solely related to disease progression is not considered an SAE. Hospitalization for an elective or planned procedure to treat a pre-existing condition is not considered an SAE unless it results in one of the outcomes listed above.

6.2.1.3.2. Intensity

Investigators need to assess the severity of AEs according to the guidelines provided in NCI-CTCAE, version 4.03.

CTCAE v 4.03 Severity Grades are:

- Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated; mild AE
- Grade 2: Moderate; minimal, local or non-invasive intervention indicated; limiting age-appropriate instrumental activities of daily living; moderate AE

- Grade 3: Severe or medically significant but non immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living; severe AE
- Grade 4: Life-threatening consequences; urgent intervention indicated
- Grade 5: Fatal AE

If the AE is not specified in the CTCAE or the study protocol, the grading of severity will be assessed as mild (Grade 1), moderate (Grade 2), severe (Grade 3), life-threatening (Grade 4), or death due to the AE (Grade 5) using the following definitions:

- Mild: The patient is aware of the event or symptom, but the event or symptom is easily tolerated.
- Moderate: The patient experiences sufficient discomfort to interfere with or reduce his or her usual level of activity.
- Severe: Significant impairment of functioning: the patient is unable to carry out usual activities.
- Very severe (life-threatening): The patient's life is at risk from the event.

6.2.1.3.3. Causality

The Investigator will assess the causality/relationship between the study drug and the AE and record that assessment on the eCRF.

The most likely cause of an SAE (e.g., disease under treatment, concomitant disease, concomitant medication, other) will be indicated on the eCRF with details of the concomitant disease or medication or other cause.

The relatedness for SAEs will also be assessed and documented on the SAE form. Table 6 provides guidance for assessing the causal relationship to the investigational product.

Table 6: Causal Attribution Guidance

Is the Adverse Event/Serious Adverse Event suspected to be caused by the investigational product based on facts, evidence, science-based rationales, and clinical judgment?	
Yes	The temporal relationship of the AE to investigational product administration makes a causal relationship possible, **and** other drugs, therapeutic interventions, or underlying conditions do not provide sufficient explanation for the AE.
No	The temporal relationship of the AE to investigational product administration makes a causal relationship unlikely, **or** other drugs, therapeutic interventions, or underlying conditions provide a sufficient explanation for the AE.

Note: The Investigator's assessment of causality for individual AE reports is part of the study documentation process. Regardless of the "Yes" or "No" causality assessment for individual AE reports, the Sponsor will promptly evaluate all reported SAEs against cumulative product experience to identify and expeditiously communicate possible new safety findings to Investigators and applicable regulatory authorities.

6.2.1.3.4. Outcome and Action Taken

The Investigator will record the action taken and outcome for each AE according to the following criteria:

- Action Taken
  - None
  - Dose reduced
  - Administration of FPA008 temporarily interrupted
  - Administration of FPA008 permanently discontinued
  - Concomitant medication
  - Other
- Outcome
  - Recovered without sequelae
  - Recovered with sequelae
  - Ongoing
  - Death
  - Unknown/Lost to follow-up

6.2.1.4. Recording Adverse Events

Any new symptoms or injury or worsening of symptoms that occur following signing of the ICF, but prior to the first infusion (Cycle 1, Day 1), will be considered pretreatment events and reported on the Medical History page of the eCRF, unless they directly correlate to a study-related procedure. New or worsening symptoms or injury related to study-related procedures that occur before Cycle 1, Day 1 will be reported as adverse events. Otherwise, adverse event reporting will begin on Cycle 1, Day 1 (day of first infusion) and continue through the End of Treatment Follow-up Period or until 90 days (±7 days) after the last dose of study drug. Serious AEs occurring after the end of the study should be reported to the Sponsor by the Investigator if the Investigator considers there is a causal relationship with the study drug.

All AEs, regardless of the relationship to study drug, will be recorded on the eCRF. This includes potential end-organ toxicity, e.g., renal (proteinuria), hepatic, and cardiovascular (increased blood pressure) effects, and effects on wound healing. All AE reports should contain a brief description of the event, date and time of onset, date and time of resolution, intensity, treatment required, relationship to study drug, action taken with the study drug, outcome, and whether the event is classified as serious.

Abnormal laboratory findings that are not considered clinically significant will be recorded only on the laboratory eCRF pages and not on the AE pages. Abnormal laboratory results that are

considered clinically significant in the Investigator's opinion are also to be recorded on the AE page of the eCRF. Relationship (reasonable causal relationship) to drug therapy and counter measures undertaken will be noted on the eCRF.

6.2.1.5. Reporting Serious Adverse Events

Any SAEs, whether or not considered related to treatment with FPA008, must be reported, by the Investigator, to the Sponsor (and/or designee) within 24 hours of the Investigator becoming aware of the event and will be recorded on both the SAE form and AE page of the eCRF. Additional SAE information including medications or other therapeutic measures used to treat the event, action taken with the study drug due to the event, and outcome/resolution of the event will be recorded on the SAE form. Forms for reporting SAEs will be provided to the study sites.

A copy of SAE forms must be faxed **within 24 hours** to the attention of the [redacted] Pharmacovigilance Safety Specialist:

[redacted]

The Investigator should not wait to receive additional information to fully document the event before notification of a SAE, though additional information may be requested. The minimum information that is required for an initial SAE report is as follows:

- Patient number
- Investigator name and site number
- Event term
- Event onset date
- Serious criteria
- Relationship to study drug

As applicable, information from relevant laboratory results, hospital case records, and autopsy reports should be obtained.

The Investigator and Sponsor (and/or designee) will review each SAE report and evaluate the seriousness and causal relationship of the event to study treatment. In the event of a disagreement about causality, the greater level of assessment will be used. In addition, the Sponsor will evaluate the expectedness according to the FPA008 IB. Based on the Investigator and the Sponsor's assessment of the event, a decision will be made concerning the need for further action.

The Sponsor (or designee) is responsible for submitting reports of AEs associated with the use of the drug that are both serious and unexpected to FDA, according to 21 Code of Federal Regulations (CFR) 312.32, and to other regulatory authorities, according to national law and/or local regulations. All Investigators participating in ongoing clinical studies with the study medication will receive copies of these reports for prompt submission to their Institutional Review Board (IRB) or Independent Ethics Committee (IEC).

The Sponsor (or designee) will submit all safety updates and periodic reports to the regulatory authorities as required by applicable regulatory requirements.

6.2.1.6. Follow-up of Adverse Events

All AEs experienced by a study patient, irrespective of the suspected causality, will be monitored until the event has resolved or stabilized, any abnormal laboratory values have returned to baseline or stabilized at a level acceptable to the Investigator and Medical Monitor, there is a satisfactory explanation for the changes observed, or the patient is lost to follow-up.

6.2.1.7. Pregnancy

Pregnancy tests should be performed for any patient of childbearing potential, as noted in Appendix 1. In the event of suspected pregnancy, the pregnancy test should be repeated. Patients who become pregnant during the study must discontinue study treatment immediately.

ICON Pharmacovigilance must be notified of any patient that becomes pregnant while participating in this study. Although pregnancy is not an AE, all pregnancies must be followed to conclusion to determine their outcome. It is the responsibility of the Investigator or designee to report any pregnancy in a patient that occurs during the study by completing the Pregnancy Reporting Form. Please contact the study monitor to receive the Pregnancy Reporting Form on learning of a pregnancy.

Notification of the pregnancy including the anticipated date of birth should be submitted on a Pregnancy Reporting Form within 24 hours of awareness and reported using the same procedure as described for reporting SAEs (Section 6.2.1.5). If the pregnancy is to be terminated, the anticipated date of termination should be provided.

6.2.1.7.1. Follow-up in the Event of a Pregnancy

The patient will be asked to provide information on the outcome of the pregnancy, including premature termination should the case arise. Spontaneous miscarriages and congenital abnormalities will be reported as SAEs. Information on the status of the mother and child will be forwarded to ICON Pharmacovigilance and the Sponsor. Generally, follow-up will be in accordance with regulatory guidance and at least 6 to 8 weeks after the estimated delivery date. Any premature termination of the pregnancy will be reported as an SAE.

6.2.2. Laboratory Parameters

Laboratory assessments will be performed locally at each study site's laboratory by means of their established methods. Before starting the study, the Investigator will provide the Sponsor (and/or designee) with a list of the normal ranges and units of measurement.

Blood samples should be taken using standard venipuncture techniques. The following laboratory parameters Table 7) will be determined in accordance with the Schedule of Assessments (Appendix 1):

Table 7: Laboratory Assessments

Hematology: Complete blood cell (CBC) with differential: white blood cells (WBC) ANC neutrophils (%) eosinophils (%) basophils (%) lymphocytes (%) monocytes (%) platelets hemoglobin hematocrit red blood cells (RBC) RBC indices: mean corpuscular volume (MCV) mean corpuscular hemoglobin (MCH) mean corpuscular hemoglobin concentration (MCHC)
Urinalysis: Dipstick (appearance, color, pH, specific gravity, ketones, protein, glucose, bilirubin, nitrite, urobilinogen, and occult blood) If dipstick is positive (2+ or greater) for blood or protein, perform a microscopic examination.
Clinical chemistry: albumin glucose lactate dehydrogenase (LDH) Troponins (cardiac and skeletal) blood urea nitrogen (BUN) calcium chloride carbon dioxide (CO_2) creatinine direct bilirubin phosphate alkaline phosphatase ALT (SGPT) AST (SGOT) CK isoenzymes (if CK abnormal)* potassium sodium total bilirubin total cholesterol total protein uric acid CK (creatinine kinase) * Refer to Table 4 for reflex testing of CK isoenzymes if CK is elevated.
Other chemistry tests: Magnesium
Coagulation: INR PT APTT
Serum pregnancy test: For females of childbearing potential only.
Other test: **Antinuclear antibodies (ANA)**

Abnormal laboratory results that lead to a change in patient treatment management (e.g., dose delay, requirement for additional medication or monitoring) are considered clinically significant for the purposes of this study and will be recorded on the AE page of the eCRF. Values meeting SAE criteria must be reported as SAEs.

The Investigator's determination of relationship of the AE to drug therapy and counter measures undertaken will be documented and noted on the eCRF.

6.2.3. Vital Signs

Vital signs will include sitting blood pressure, pulse, respiration rate, and temperature. All vital signs will be obtained after the patient has been resting for at least 5 minutes. Vital signs will be performed in accordance with the Schedule of Assessments (Appendix 1).

6.2.4. Electrocardiograms

Twelve-lead ECGs will be performed in accordance with the Schedule of Assessments (Appendix 1). The Investigator must review the ECG, document this review in the source documents, and record any clinically significant changes that occur during the study as an AE in the eCRF.

6.2.5. Pregnancy

Pregnancy is an exclusion criterion and women of childbearing potential must not be considering getting pregnant during the study. A negative serum pregnancy test fewer than 5 days prior to first dosing with FPA008 treatment is mandatory. Patients of reproductive potential (males and females) must practice 2 effective contraception methods (Section 4.2) during the study and for 6 months after last treatment.

6.2.6. Physical Examinations

Physical examinations will be performed in accordance with the Schedule of Assessments (Appendix 1).

A complete physical examination including height and weight will be performed at Screening. Complete physical examinations should be conducted per the Schedule of Events (Appendix 1).

6.2.7. Immunogenicity

Immunogenicity, defined as an immune response to FPA008, will be assessed by measurement of total anti-FPA008 antibodies from all patients. Immunogenicity testing will consist of screening, confirmation, and titration.

Samples for immunogenicity assessment will be drawn from each patient at the time points designated in Appendix 2. Samples for immunogenicity testing will be collected and processed according to the instruction provided in the Laboratory Manual.

6.2.8. ECOG Performance Status

ECOG performance status will be assessed at Screening, within 72 hours prior to dosing on Day 1 of each cycle, and through the End of Treatment Follow-up Period (Appendix 1).

6.3. Pharmacokinetic Parameters

In this study, samples for the determination of serum FPA008 will be collected as outlined in Appendix 2. The sampling will allow determination of the exposure (AUC), C_{max}, C_{min} (trough concentration), CL, and V_{ss}. Other PK parameters, such as accumulation ratio and half-life, may also be calculated as data allow.

These samples will be collected and processed according to the instructions provided in a separate Laboratory Manual.

6.4. Pharmacodynamic Parameters

[redacted]

The following procedures (see Appendix 1) only apply to patients who sign the applicable Optional Research Informed Consent Form; the purpose of these procedures is to understand the impact of FPA008 on changes in local biomarkers of inflammation (synovium and synovial fluid) and distribution of FPA008 to the involved joint (synovial fluid):

- Synovium (optional)
  - [redacted]
- Synovial fluid (optional)
  - FPA008 concentration; cellular component for above markers by IHC.

6.5. Patient and Clinician Reported Outcome Measures

Clinical assessment of health outcomes (function, symptoms) will be done at Screening, C1D15 (pre-dose), C2D1 (pre-dose), and then on Day 1 (pre-dose) for all subsequent cycles through 24 weeks of treatment or until treatment is discontinued, and through the End of Treatment Follow-up Period. Patients who have not progressed and enter Long-Term Follow-up are to be followed every 14 weeks (± 2 weeks) until progression, the patient undergoes local therapy

(e.g., resection, radiation) or a new systemic therapy is initiated, for up to 52 weeks following C1D1. The following tools will be used to collect exploratory endpoint data on symptom and functional outcomes:

- Ogilvie-Harris (OH) Scale (Appendix 4): This tool was developed specifically for patients with PVNS (Ogilvie-Harris 1992) and has been used in other PVNS publications (De Ponti 2003, Rhee 2010). Characteristics of this tool include the following:
  - It is a clinician reported outcome measure
  - It is based on a 0–3 interval scale for each of the 4 domains:
    - Pain
    - Synovitis/effusion
    - Range of motion
    - Functional capacity
  - It uses lower end of the scale (score min = 0) indicating severe disability, pain and functional loss and the higher values (score max = 12) indicating no disability. Scores can be summed and classified as follows:
    - Poor condition (0 – 3 points)
    - Fair condition (4 – 6 points)
    - Good condition (7 – 9 points)
    - Excellent condition (10 – 12 points)
- Brief Pain Inventory (Appendix 5): The Brief Pain Inventory rapidly assesses the severity of pain and its impact on functioning, has been translated into dozens of languages, and has been widely used in research and clinical settings in a variety of cancer and non-cancer studies. Characteristics of this tool include the following:
  - Assesses severity of pain and impact of pain on daily functions
  - Has been validated in patients with chronic and acute pain
  - Assesses the severity of pain, impact of pain on daily function, location of pain, pain medications and amount of pain relief in the past 24 hours or past week
  - Assesses responsiveness of behavioral and pharmacological pain intervention
  - Can be completed either by self-report or interview
  - Takes approximately five minutes to complete
  - Questions are scored from 0 (least or does not interfere) to 10 (worst or completely interferes).

  - No scoring algorithm, but "worst pain" or the arithmetic mean of the four severity items can be used as measures of pain severity or interference
  - Reliability (Cronbach alpha reliability) ranges from 0.77 to 0.91
- Joint Stiffness Numeric Rating Scale (Appendix 6)
  - Is a patient reported outcome (PRO) measure which evaluates stiffness
    - Is a 10 point stiffness rating scale in which the patient is asked to make 3 stiffness ratings corresponding to the current, least and worst pain experiences over the past 24 hours
    - The average of the 3 ratings is used to represent the patient's level of stiffness over the previous 24 hours.

7. Study Conduct

7.1. Overview of Patient Assessments

After an initial Screening period of up to 28 days (4 weeks), patients will be treated with FPA008 every 2 weeks (± 3 days) in 28-day cycles, and FPA008 will be administered over approximately 30 minutes. All time points of assessments should be completed in the timeframe stated. Assessments performed prior to the patient signing the informed consent are acceptable only if confirmed to have been standard of care.

The schedule of detailed patient assessments is shown in Appendix 1 and Appendix 2. Instructions for the sampling and processing of PK, PD, and immunogenicity data are described in a separate, protocol-specific laboratory manual.

7.2. Study Assessments and Procedures by Visit

7.2.1. Screening Period (Day –28 to Day 0)

Patients who have fully consented to participation in the study will undergo Screening assessments within 28 days (4 weeks) prior to administration of the first infusion of FPA008 (unless otherwise stated). To determine if the patient meets all the inclusion criteria and does not violate the exclusion criteria, the following procedures will be performed (Appendix 1):

- Written, signed informed consent must be collected prior to any study-specific procedures
- Complete medical and disease history
- Demographic and baseline characteristics
- Vital signs (sitting blood pressure, pulse, respiration rate, and temperature [°C] after 5 minutes rest)
- Complete physical examination, including height and weight
- ECOG performance status evaluation
- 12-lead ECG (required at Screening, and if clinically indicated during the study)
- AE reporting, if applicable
- Document prior and concurrent medications
- Quantiferon test (for latent TB)
- Clinical safety labs as outlined in Table 7 (including ANA)
- Ogilvie-Harris, Brief Pain Inventory, and Joint Stiffness Numeric Rating Scale assessments
- Optional archival tissue
- Optional synovial biopsy

- Optional synovial fluid aspirate
- Serum pregnancy test (beta-human chorionic gonadotropin [β-HCG]), ≤ 5 days prior to Cycle 1, Day 1, for women of childbearing potential
- Radiological imaging: MRI of the involved joint(s) is to be performed within 28 days prior to the first infusion of FPA008. If the MRI is performed as part of the patient's standard of care within 28 days of the first study infusion it does not need to be repeated if the documentation of results is provided and is adequate for an assessment.
- PET scan of the involved joints from a subset of approximately 10 patients in Phase 2

***Note*:** A protocol-specific patient registration form must be submitted to the Sponsor (or designee) to confirm patient eligibility prior to initiation of study treatment.

7.2.2. Treatment Allocation (Dosing Assignment)

This is an open-label study. Enrollment numbers will be faxed or emailed to the Investigator (or designee). The Sponsor (or designee) will maintain records of the number of patients treated within a specific cohort and will determine to which treatment cohort newly enrolled patients will be assigned.

7.2.3. Phases 1, 2 and Retreatment Cohort: Cycle 1, Day 1

The following procedures will be performed:

- Prior to FPA008 infusion (within ≤ 72 hours unless otherwise stated):
  - Verification of eligibility
  - Update medical and disease history to capture any changes from Screening
  - AE reporting, if applicable
  - Review of concomitant medications
  - Record weight
  - Vital signs (sitting blood pressure, pulse, respiration rate, and temperature [°C] after 5 minutes rest)
  - ECOG performance status evaluation
  - Clinical safety labs with the exception of urinalysis and ANA as outlined in Table 7
  - Serum ß-hCG (evaluated by local laboratories) will be performed ≤ 5 days prior to the first dose of FPA008 only on women of childbearing potential
  - PK, ADA, serum biomarkers and $CD14^{+}/CD16^{+}$ monocytes sample collections (within ≤ 4 hours) as outlined in Appendix 2
- Study drug administration: Administer FPA008, by IV infusion over approximately 30 minutes

- Post FPA008 administration:
  - PK, serum biomarkers and $CD14^+/CD16^+$ monocytes sample collections (± 5 min) as outlined in Appendix 2
  - Post-dose Vital signs (sitting heart rate, blood pressure, respiration rate, and temperature [°C] after 5 minutes rest) at the following time points after completion of the IV infusion:
  - 5 minutes (± 5 minutes), 15 minutes(± 5 minutes), 30 minutes(± 5 minutes), and 1 hour (± 5 minutes)
  - AE reporting, if applicable
  - Review of concomitant medications

7.2.4. Phases 1, 2 and Retreatment Cohort: Cycle 1, Day 2

- PK, serum biomarkers, and $CD14^+/CD16^+$ monocytes sample collections as outlined in Appendix 2
- AE reporting, if applicable
- Review of concomitant medications

7.2.5. Phases 1, 2 and Retreatment Cohort: Cycle 1, Day 8

Study patients will return to the study center on Day 8 (± 2 days). No treatment will be administered.

The following assessments will be completed:

- Vital signs (sitting blood pressure, pulse, respiration rate, and temperature [°C] after 5 minutes rest)
- Clinical safety labs with the exception of ANA, as outlined in Table 7
- PK, serum biomarkers, $CD14^+/CD16^+$ monocytes sample collections as outlined in Appendix 2
- AE reporting, if applicable
- Review of concomitant medications

7.2.6. Phases 1, 2 and Retreatment Cohort: Cycle 1, Day 15

Study patients will return to the study center on Day 15, and the following assessments will be completed.

- Prior to FPA008 infusion (within ≤ 72 hours unless otherwise stated):
  - Record weight
  - Vital signs (sitting blood pressure, heart rate, respiration rate, and temperature [°C] after 5 minutes rest)

  - Clinical safety labs with exception of urinalysis and ANA as outlined in Table 7
  - Ogilvie-Harris, Brief Pain Inventory, and Joint Stiffness Numeric Rating Scale PK, ADA, serum biomarkers and $CD14^{+}/CD16^{+}$ monocytes sample collections (within ≤ 4 hours) as outlined in Appendix 2
  - Update medical and disease history
  - AE reporting, if applicable
  - Review of concomitant medications
- Study drug administration: Administer FPA008, by IV infusion over 30 minutes
- Post FPA008 administration:
  - PK sample collection 15 minutes (±5 min) after end of infusion (as outlined in Appendix 2)
  - Post-dose Vital signs (sitting heart rate, blood pressure, respiration rate, and temperature [°C] after 5 minutes rest) at the following time points after completion of the IV infusion:
  - 5 minutes (± 5 minutes), 15 minutes (± 5 minutes), 30 minutes (± 5 minutes), and 1 hour (± 5 minutes)
  - 12-lead ECG (within approximately 30 minutes post-dose after PK/PD sample collection)
  - AE reporting, if applicable
  - Review of concomitant medications

7.2.7. Phase 1: End of Cycle 1

For Phase 1 patients, if at the end of Cycle 1 the Investigator determines that the patient may benefit from continued dosing with FPA008, entry into the Extended Treatment Period may be offered.

If the patient is continuing onto the Extended Treatment Period (Cycle 2 and beyond), proceed to procedures outlined in Section 7.2.8.

If the patient does not qualify to receive further doses of FPA008, the patient will return to the clinic for the End of Treatment Follow-up Visits.

7.2.8. Phase 1 Extended Treatment/Phase 2 and Retreatment Cohort Cycle 2 and Subsequent Cycles

Phase 1 Extended treatment may begin on Cycle 2, Day 1. Dosing will be discontinued if the patient experiences either disease progression or unacceptable toxicity.

At each infusion visit, patients are to remain at the study site after each administration of FPA008 until completion of all post-dose assessments for safety monitoring. The following assessments will be performed at each visit unless otherwise noted (Appendix 1):

7.2.8.1. Phases 1 and 2 and Retreatment Cohort: Cycle 2 and Subsequent Cycles, Day 1

- Prior to each infusion of study drug (within ≤72 hours unless otherwise stated):
  - Vital signs (sitting heart rate, blood pressure, respiration rate, and temperature [°C] after 5 minutes rest)
  - Complete physical examination including weight at Cycle 2, 4, and 6
  - ECOG performance status evaluation
  - Ogilvie-Harris, Brief Pain Inventory, and Joint Stiffness Numeric Rating Scale
  - Clinical safety labs with the exception of urinalysis and ANA as outlined in Table 7
  - PK, ADA, serum biomarkers and $CD14^{+}/CD16^{+}$ monocytes sample collections (within ≤ 4 hours) on Day 1 of Cycles 2, 3, and 5 as outlined in Appendix 2
  - MRI of the involved joint(s) using the same physical or radiologic parameter(s) used to evaluate baseline tumor measurements are to be done within 1 week of C2D1, C3D1, and C5D1
  - Optional synovial biopsy up to -2 days prior to dose administration (Cycle 2 only) as outlined in Appendix 1
  - Optional synovial fluid aspirate up to -2 days prior to dose administration (Cycle 2 only) as outlined in Appendix 1
  - AE reporting, if applicable
  - Review of concomitant medications
- Study drug administration: Administer FPA008, by IV infusion over approximately 30 minutes
- Post study drug administration:
  - Post-dose Vital signs (sitting heart rate, blood pressure, respiration rate, and temperature [°C] after 5 minutes rest) at the following time points after completion of the IV infusion:
  - 5 minutes (± 5 minutes), 15 minutes(± 5 minutes), 30 minutes (± 5 minutes), and 1 hour (± 5 minutes)
  - PK sample collection 15 minutes (±5 min) after end of infusion on Day 1 of Cycles 3, and 5 (Appendix 2)
  - AE reporting, if applicable
  - Review of concomitant medication
  - PET scan of the involved joints from a subset of approximately 10 patients at the Cycle 3 Day 1 (±7 days),

7.2.8.2. Phases 1 and 2 and Retreatment Cohort: Cycle 2 and Subsequent Cycles, Day 15

- Prior to each infusion of study drug (within ≤72 hours unless otherwise stated):
  - Vital signs (sitting heart rate, blood pressure, respiration rate, and temperature [°C] after 5 minutes rest)
  - Clinical safety labs with the exception of urinalysis and ANA as outlined in Table 7
  - AE reporting, if applicable
  - Review of concomitant medications
  - PET scan of the involved joints from a subset of approximately 10 patients at the Cycle 6 Day 15 visit (±7 days) in Phase 2
- Study drug administration:
  - Administer FPA008, by IV infusion over approximately 30 minutes
- Post study drug administration:
  - Post-dose Vital signs (sitting heart rate, blood pressure, respiration rate, and temperature [°C] after 5 minutes rest) at the following time points after completion of the IV infusion:
  - 5 minutes (± 5 minutes), 15 minutes(± 5 minutes), 30 minutes(± 5 minutes), and 1 hour (± 5 minutes)
  - 12-lead ECG (within approximately 30 minutes post-dose after PK/PD sample collection)
  - AE reporting, if applicable
  - Review of concomitant medication

7.2.9. End of Treatment Follow-up Period

Patients will return to the study center three times, approximately 30 days (±7 days), 60 days (±7 days), and 90 days (±7 days) after their last infusion of FPA008, to complete the End of Treatment Follow-up Period.

The following assessments will be performed:

- Vital signs (sitting pulse, blood pressure, respiration rate, and temperature [°C] after 5 minutes rest)
- 12-lead ECG at the 30 days (±7 days) End of Treatment Follow-up Visit only
- Complete physical examination at the 30 days (±7 days) End of Treatment Follow-up Visit only. Weight is to be recorded at all visits.
- ECOG performance status evaluation
- Clinical safety labs as outlined in Table 7 (including ANA at the 30 days (±7 days) End of Treatment Follow-up Visit only)

- PK, ADA, serum biomarkers and $CD14^+/CD16^+$ monocytes sample collections as outlined in Appendix 2
- Serum ß-hCG (evaluated by local laboratories) in women of child-bearing potential
- MRI of the involved joint(s), Ogilvie-Harris, Brief Pain Inventory, and Joint Stiffness Numeric Rating Scale assessments at the 30 days (±7 days) and 90 days (±7 days) End of Treatment Follow-up Visits. These can be omitted if performed within 6 weeks prior or if tumor progression was previously determined.
- PET scan of the involved joint from a subset of approximately ten patients in Phase 2 at the 90 days (±7 days) End of Treatment Follow-up Visit only
- AE reporting, if applicable
- Review of concomitant medications

7.2.10. Long-Term Follow-up Period

Patients who have not progressed should continue onto Long-Term Follow-up after completing the End-of-Treatment Follow-up Period. Patients will be followed every 14 weeks (± 2 weeks) until progression, the patient undergoes local therapy (e.g., resection, radiation) or a new systemic therapy is initiated, for up to 52 weeks following C1D1.

The following assessments will be performed:

- Clinical safety labs with the exception of urinalysis and ANA
- PK, ADA, serum biomarkers and $CD14^+/CD16^+$ monocytes sample collections as outlined in Appendix 2
- MRI of the involved joint(s), Ogilvie-Harris, Brief Pain Inventory, and Joint Stiffness Numeric Rating Scale Assessments
- PET scan of the involved joint from a subset of approximately ten patients in Phase 2 at the first Long-Term Follow-up Visit (14 weeks (± 2 weeks) post 90 days End of Treatment Visit)
- AE reporting for ongoing adverse events thought to be related to study treatment, if applicable
- Reporting of concomitant medications (local therapy (e.g., resection, radiation) or a new systemic therapy only)

8. Statistical Methods

Before database lock, a separate statistical analysis plan (SAP) will be finalized, providing detailed methods for the analyses outlined below.

Any deviations from the planned analyses will be described and justified in the final integrated study report.

8.1. Study Patients

8.1.1. Disposition of Patients

The number and percentage of patients evaluable for DLT, safety, efficacy, PK and PD will be presented. Reasons for withdrawal will also be summarized.

8.1.2. Protocol Deviations

A summary of the number and percentage of patients with protocol deviations by type of deviation will be provided. Deviations will be defined in the SAP prior to database lock.

8.1.3. Analysis Populations

The following analysis populations are defined for the study:

- Safety Population—all patients who have received any portion of at least one dose of FPA008.
- DLT-Evaluable Population—all patients enrolled into Phase 1 of the study who received at least 2 doses of FPA008 and completed Cycle 1 of treatment, or who experienced a DLT in Cycle 1.
- PK-Evaluable Population—all patients who have received at least one dose of FPA008 and have had adequate PK assessments drawn for determination of the PK profile.
- Efficacy-Evaluable Population—all patients who met eligibility criteria, received at least 1 dose of FPA008, have measurable tumor lesions at baseline, and have at least 1 post-baseline disease assessment.
- Intent-to-Treat Population (ITT)—all enrolled patients. Patient without post-baseline disease assessment will be considered as non-responder.

8.2. General Considerations

All analyses will be descriptive and will be presented by phase, dose group, and overall as appropriate. Patients dosed at the RD will be summarized, except the Retreatment Cohort data will be summarized separately from the naïve patient data from Phase 2. Data collected in this study will be presented using summary tables and patient data listings. Continuous variables will be summarized using descriptive statistics, specifically the number of valid cases, arithmetic

mean, median, standard deviation (SD), minimum, and maximum. Categorical variables will be summarized by frequencies and percentages.

A change to the data analysis methods described in the protocol will require a protocol amendment only if it alters a principal feature of the protocol. The SAP will be finalized prior to database lock. Any changes to the methods described in the final SAP will be described and justified in the clinical study report.

8.3. Demographics, Baseline Characteristics, and Concomitant Medications

Demographic data, medical history, other baseline characteristics, concomitant disease, and concomitant medication will be summarized by cohort and overall. To determine whether the criteria for study conduct are met, corresponding tables and listings will be provided. These will include an assessment of protocol deviations, study drug accountability, and other data that may impact the general conduct of the study.

8.4. Treatment Compliance

Treatment administration will be summarized by cohort including dose administration, dose modifications or delays, cumulative dose, average dose, number of infusions, and the duration of therapy.

8.5. Analyses of Tumor Response

Patients will be classified according to their best overall tumor response (complete response [CR], partial response [PR], stable disease [SD], or progressive disease [PD]). Frequencies, proportions, and exact 95% CI of patients, when appropriate, stratified by their best overall tumor response will be calculated. Patients with a best overall tumor response of CR or PR with duration of at least 4 weeks (28 days) will be further classified as having an objective tumor response. Listing of patients with an objective tumor response will be presented.

Patients will be classified for response by RECIST 1.1 and the Total Volume Score. The Tumor Volume Score classifies response according to the following definitions: Complete Response [(CR) lesion completely gone by the end of the study], Partial Response [(PR) ≥50% decrease in volume score relative to baseline], Progressive Disease [(PD) ≥30% increase in volume relative to lowest score during the study whether at baseline or some other visit] or Stable Disease [(SD) does not meet any of the prior criteria based on score during study].

In addition to local review, all MRI scans will be centrally reviewed, and concordance between the local and central assessments of tumor response will be determined.

Duration of response by RECIST 1.1 will be calculated as the number of days from the first documentation of overall response (CR or PR) to the first documentation of disease progression or death, whichever comes first. Patients who are alive and progression-free at the time of data analysis will be censored at the time of their last assessment for tumor response.

In patients who respond adequately such that a decision is made to resect residual disease, the duration of response will be censored at the time of the surgical procedure.

In addition to the MRI assessments, approximately ten patients from Phase 2 will have PET assessments which will be locally reviewed according to RECIST guidelines, observing change in normalized SUV for lesions in the affected joints.

8.6. Safety Analyses

Safety analyses will be performed separately within both phases of the study and for all patients combined. Data from all patients that receive any portion of at least 1 dose of FPA008 will be included in the safety analyses. AEs, clinical laboratory information, vital signs, ECOG performance status, weight, ECGs, and concomitant medications/procedures will be tabulated and summarized.

AEs will be summarized overall and with separate summaries for serious AEs, AEs leading to discontinuation, AEs leading to death, and NCI CTCAE Version 4.03 Grade 3 or higher AEs.

Weight and vital signs will be summarized descriptively (N, mean, standard deviation, median, minimum, and maximum). ECOG performance status will be summarized categorically and descriptively.

Shift tables displaying patient counts and percentages classified by baseline grade and maximum grade on treatment will be provided for laboratory data by cohort and overall. A marked laboratory change is defined as a shift from a baseline Grade 0 to Grade 3 (non-hematologic) or Grade 4 (hematologic) on treatment, or a shift from a baseline Grade 1 to Grade 4 on treatment. The number and percentage of patients with marked laboratory changes will be tabulated by cohort and overall.

8.7. Efficacy Analysis

Efficacy analyses will be descriptive. All patients dosed at the RD, including patients from both Phase 1 and 2, will also be summarized. The overall response rate will be summarized with frequencies and percentages. The duration of response for CR and PR patients will be summarized with descriptive statistics (N, arithmetic mean, standard deviation, median, minimum, and maximum) as well as categorically. Response and duration of response will be determined using RECIST 1.1. Kaplan-Meier methodology will be used to summarize duration of response.

8.8. Pharmacokinetic Analyses

Individual and mean (±SD) serum FPA008 concentration-time data will be tabulated and plotted by dose level. FPA008 PK parameters will be calculated from the serum drug concentration-time data using a non-compartmental analysis (NCA) method with intravenous infusion input in [redacted] Alternative methods may be considered.

Estimated individual and mean (±SD) PK parameters will be tabulated and summarized by dose level. Other descriptive statistics might be reported for serum FPA008 concentration-time data and estimated PK parameters. Dose proportionality, drug accumulation, and attainment of steady state will be evaluated whenever it is possible.

The impact of immunogenicity on FPA008 exposure will be assessed.

8.9. Interim Analyses

No formal interim analysis is planned.

Safety data will be reviewed on a routine basis by the Sponsor and CRO. In Phase 1, the Sponsor (and/or designee) and Investigator(s) will review safety data from each dose cohort prior to dose escalation or de-escalation. Adverse event data from the extended treatment period will be presented to the medical monitors when available.

8.10. Determination of Sample Size

Three patients per dose group, with a sample size increase to 6 in the case of DLT, is generally accepted as adequate to determine the safety of escalating doses of novel oncologic drugs. If a DLT is observed in 1 of 3 patients, then 3 additional patients will be enrolled at that same dose level. Dose escalation will continue until 2 of 3–6 patients treated at a dose level experience a DLT. The MTD is defined as the maximum dose at which < 33% of patients experience a DLT during Cycle 1. After the MTD is determined, additional patients may be recruited at that dose level to further characterize the safety, PK, PD, and preliminary efficacy of FPA008. It is anticipated that 12-15 patients may be enrolled in Phase 1.

For the objective of estimating the ORR of FPA008 in patients with PVNS/dt-TGCT, it is estimated that approximately 25-30 naïve patients will be enrolled in Phase 2.In addition, a total of approximately 20 to 30 patients will be enrolled at the RD overall. The following Table 8 displays the corresponding two-sided 95% CI and the precision for various sample sizes and observed response rates (Agresti 1998).

Table 8: Two-Sided 95% CIs of the Observed Response Rates

Sample Size	Observed Response Rate	95% CI	Precision (longest one-sided CI length*)
30	15/30 (50%)	33.2% to 66.9%	~17%
	16/30 (53%)	36.1% to 69.8%	~17%
	17/30 (57%)	39.2% to 72.6%	~18%
	18/30 (60%)	42.3% to 75.4%	~18%
	19/30 (63%)	45.5% to 78.2%	~17%
	20/30 (67%)	48.7% to 80.9%	~18%
	21/30 (70%)	52.0% to 83.5%	~18%
	22/30 (73%)	55.4% to 86.0%	~18%
	23/30 (77%)	58.8% to 88.5%	~18%
	24/30 (80%)	62.3% to 90.9%	~18%
25	13/25 (52%)	31.3% to 72.2%	~20%
	14/25 (56%)	34.9% to 75.6%	~21%
	15/25 (60%)	38.7% to 78.9%	~21%
	16/25 (64%)	42.5% to 82.0%	~22%
	17/25 (68%)	46.5% to 85.1%	~22%
	18/25 (72%)	50.6% to 87.9%	~21%
	19/25 (76%)	54.9% to 90.6%	~21%
	20/25 (80%)	59.3% to 93.2%	~21%
20	11/20 (55%)	31.5% to 76.9%	~24%
	12/20 (60%)	36.1% to 80.9%	~24%
	13/20 (65%)	40.8% to 84.6%	~24%
	14/20 (70%)	45.7% to 88.1%	~24%
	15/20 (75%)	50.9% to 91.3%	~24%
	16/20 (80%)	56.3% to 94.3%	~24%
	17/20 (85%)	62.1% to 96.8%	~24%

* Distance from the observed response rate to the lower or upper CI boundary

9. Ethical, Legal, and Administrative Aspects

9.1. Data Quality Assurance

The Sponsor (or designee) may conduct a site visit prior to study initiation at a site to verify the qualifications of each Investigator, inspect the site facilities, and inform the Investigator of responsibilities and for ensuring study compliance and procedures for adequate and correct documentation.

The Investigator is required to prepare and maintain adequate and accurate case histories designed to record all observations and other pertinent data for each study patient. All information recorded on the eCRFs for this study must be consistent with the patients' source documentation (i.e., medical records).

9.2. Electronic Case Report Forms and Source Documentation

All data obtained during this study should be entered into the eCRFs promptly. All source documents from which eCRF entries are derived should be placed in the patient's medical records. eCRF fields for which source documents will typically be needed include laboratory assessments, physical exam reports, nursing notes, ECG recordings, hospital records, and MRI reports.

The eCRFs for each patient will be checked against source documents at the study site by the site monitor.

Instances of missing or uninterpretable data will be discussed with the Investigator for resolution.

9.3. Access to Source Data

During the study, a monitor will perform routine site visits to review protocol compliance, compare eCRFs and individual patient's medical records, assess drug accountability, and ensure that the study is being conducted according to pertinent regulatory requirements. eCRF entries will be verified with source documentation. The review of medical records will be performed in a manner to ensure that patient confidentiality is maintained.

In accordance with ICH GCP guidelines, the Investigator must ensure provision of sufficient time, reasonable space, and adequate qualified personnel for the monitoring visits. The visits are for the purpose of verifying adherence to the study protocol and the completeness, consistency, and accuracy of data entered on the eCRF and other documents. Moreover, regulatory authorities, IRBs, IECs, and/or the Sponsor's Quality Assurance group may wish to carry out such source data checks and/or on-site audit inspections. Direct access to source data will be required for these inspections and audits; they will be carried out giving due consideration to data protection and medical confidentiality. The Investigator assures that the Sponsor (and/or designee) will receive the necessary support to complete these activities.

All participating centers should take particular care in ensuring that original imaging source data (MRI images, echo images, etc.) are maintained and accessible for monitoring, and that these original source data are then archived on a long-term basis in compliance with ICH GCP Section 9.6. These images must be stored in a secure location until the Sponsor (or designee) authorizes their destruction, and must be retrievable by study patient number in the event of an audit.

9.4. Data Processing

The Data Management Plan, to be developed during the initiation phase of the study, will include specifications for consistency and plausibility checks on data and will also include data-handling rules for obvious data errors. All processes for data processing and query handling will be described in the Data Management Plan.

9.5. Archiving Study Records

The study site will maintain a study file, which should contain, at minimum, the Investigator's Brochure, the protocol and any amendments, the protocol for tissue sampling, drug accountability records, correspondence with the IEC/IRB and the Sponsor (or designee), and other study-related documents.

The Investigator agrees to keep records and those documents that include (but are not limited to) the identification of all participating patients, medical records, study-specific source documents, source worksheets, all original signed and dated ICFs, copies of all eCRFs, query responses, and detailed records of drug disposition to enable evaluations or audits from regulatory authorities and FivePrime or its designees.

The Investigator shall retain records required to be maintained for a period of 5 years following the date a marketing application in an ICH region is approved for the drug for the indication for which it is being investigated or, if no application is to be filed or if the application is not approved for such indication, until at least 5 years after the investigation is discontinued. However, these documents should be retained for a longer period if required by the applicable regulatory requirement(s) or if needed by the Sponsor. In addition, the Investigator must make provision for the patients' medical records to be kept for the same period of time.

No data should be destroyed without the agreement of FivePrime. Should the Investigator wish to assign the study records to another party or move them to another location, FivePrime must be notified in writing of the new responsible person and/or the new location.

Patients' medical records and other original data will be archived in accordance with the archiving regulations or facilities of the investigational site.

9.6. Good Clinical Practice

The procedures set out in this study protocol are designed to ensure that the Sponsor and Investigator abide by GCP guidelines of the ICH and the Declaration of Helsinki (1989). The study also will be carried out in compliance with local legal requirements.

9.7. Informed Consent Form

All information about the clinical study, including the patient information and the ICF, is prepared and used for the protection of the human rights of the patient according to ICH GCP guidelines and the Declaration of Helsinki.

The ICF, prepared by the Investigator with the assistance of the Sponsor, must be approved along with the study protocol by the IEC/IRB and be acceptable to the Sponsor before each patient is enrolled on the study, written informed consent will be obtained according to the regulatory and legal requirements. A copy of the signed ICF will be retained by the patient and the original will be filed in the Investigator's site file, unless otherwise agreed. The Investigator will not undertake any investigation specifically required only for the clinical study until valid consent has been obtained. The terms of the consent and when it was obtained must be documented in the source documents and in the eCRF.

If a protocol amendment is required, the informed consent form may need to be revised to reflect the changes to the protocol. If the consent form is revised, it must be reviewed and approved by the appropriate IRB/IEC, and signed by all patients subsequently enrolled in the study as well as those currently enrolled in the study.

All signed and dated Consent Forms must remain in each patient's study file and must be available for verification by study monitors at any time.

9.8. Optional Research Informed Consent Form

If the collection of archival tissue, synovial biopsy, and/or synovial fluid for optional research described in Section 3.2 is approved by the IRB/EC, patients will have the option to authorize the collection and use of these sample(s) and personal health information for additional research purposes. Signing of this consent form is not required for enrollment in the trial but is required prior to the optional research sample collection. All procedures outlined above for the review, approval, processing, and use of the Consent Form also apply to this optional research form.

In the United States, each Informed Consent Form may also include authorization allowing the Institution, Investigator, Sub-investigator, and the Sponsor to use and disclose personal health information in compliance with the HIPAA of 1996.

Signed and dated Informed Consent Form must remain in each patient's study file and must be available for verification by site monitors at any time.

9.9. Protocol Approval and Amendment

Before the start of the study, the study protocol and/or other relevant documents will be approved by the IRB/IEC and Regulatory Authorities, in accordance with local legal requirements. The Sponsor, Sponsor's agents, and Investigator must ensure that all ethical and legal requirements have been met before the first patient is enrolled in the study.

This protocol is to be followed exactly. To alter the protocol, amendments must be written, receive approval from the appropriate personnel, and receive IRB/IEC and Regulatory Authorities approval prior to implementation (if appropriate).

All amendments will be distributed to all protocol recipients, with appropriate instructions. Administrative changes (not affecting the patient benefit/risk ratio) may be made without the need for a formal amendment. Administrative changes will be distributed to the Investigator and others as appropriate.

9.10. Cohort Review Committee

The CRC will assess safety of the study on a regular basis. The CRC will consist of representatives from the Sponsor, CRO, as well as one or more designated Investigators from actively participating sites in which FPA008 is being evaluated.

9.11. Duration of the Study

For any individual patient, the minimum duration of the study will be approximately 5 months. This includes up to 28 days for Screening, 28 days on study, and 90 days of post-treatment follow-up. Patients who are considered to be benefitting from FPA008 treatment may continue on study for up to 24 weeks of treatment or until disease progression, whichever comes first.

9.12. Premature Termination of the Study

If the Investigator, Sponsor, or Medical Monitor becomes aware of conditions or events that suggest a possible hazard to patients if the study continues, the study may be terminated. The study may also be terminated early at the Sponsor's discretion in the absence of such a finding.

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

- Discovery of an unexpected, significant, or unacceptable risk to the patients enrolled in the study
- Failure to enroll patients at an acceptable rate
- Decision on the part of the Sponsor to suspend or discontinue development of the drug.

9.13. Confidentiality

All study findings and documents will be regarded as confidential. The Investigator and members of his/her research team must not disclose such information without prior written approval from the Sponsor.

The anonymity of participating patients must be maintained. Patients will be identified on eCRFs and other documents submitted to the Sponsor (or designee) by their patient number, birth date, and/or initials. Study patients are not to be identified by name, and any information sent to the Sponsor (or designee) should have patient identifiers redacted, and replaced with patient ID. Documents that include the name of the patient (e.g., the signed informed consent) must be maintained in confidence by the Investigator. The Investigator further agrees to take all reasonable precautions to prevent the disclosure by any employee or agent of the study center to any third party or otherwise into the public domain.

9.14. Other Ethical and Regulatory Issues

If a significant safety issue is identified, either from an individual case report or review of aggregate data, then the Sponsor will issue prompt notification to applicable regulatory authorities and Investigators. Investigators will then notify local IRB/IECs as deemed appropriate based on individual IRB/IEC policy.

A significant safety issue is one that has a significant impact on the course of the clinical trial or program (including the potential for suspension of the trial program or amendments to protocols) or warrants immediate update of the informed consent form.

[redacted]

[redacted]

[redacted]

11. Appendices

The following appendices are provided for this protocol.

Appendix 1: Schedule of Assessments

Procedure [a, b]	Screening	Phases 1,2, and Retreatment Cohort: Cycle 1				Phase 1 Extended Treatment Period / Phase 2 and Retreatment Cohort Cycle 2 & Subsequent Cycles		End of Treatment Follow-up Period[s]	Long-Term Follow-up Period[t]
	Day -28 to Day 0	Day 1	Day 2	Day 8	Day 15	Day 1	Day 15	30 days (± 7 days), 60 days (± 7 days) & 90 days (±7 days) post-last dose	
	Week 0	Week 1		Week 2	Week 3	≥ Week 4			
Informed Consent	×								
Review/Confirm Eligibility Criteria	×	×							
Medical History/Demographics	×	×							
Physical Examination[c]	×					×		×	
Height and Weight[d]	×	×			×	×		×	
Vital Signs[e]	×	×		×	×	×	×	×	
ECOG Performance Status	×	×				×		×	
Screening Labs[f]	×								
Clinical Safety Labs[g]	×	×		×	×	×	×	×	×
12-Lead ECG[h]	×				×		×	×	
MRI of Involved Joint(s)[i]	×					×		×	×
PET Scan[w]	×					X	×	×	×
Serum Pregnancy Test[j]	×	×						×	
Ogilvie-Harris/, Brief Pain Inventory and Joint Stiffness Numeric Rating Scale Assessments[k]	×				×	×		×	×
Optional Archival Tumor Tissue[l]	×								
Optional Synovial Biopsy[m]	×					×			
Optional Synovial Fluid Sampling[n]	×					×			
ADA Sampling[o]		×			×	×		×	×
PK and Serum Biomarkers Sampling[o]		×	×	×	×	×		×	×
[redacted]		×	×	×	×	×		×	×
Antinuclear Antibody (ANA) [q]	×							×	
FPA008 Study Drug Administration[r]		×			×	×	×		
Adverse events	×----------							×	× [u]
Prior/Concomitant Medications	×----------							×	× [v]

Notes for Schedule of Assessments

a. Unless specified, procedure is to be completed within ± 72 hours of scheduled time point and to be synchronized with administration day of FPA008 infusion.

b. Any clinical assessment, laboratory study, or additional non-specified tests may be obtained at any time, if clinically indicated.

c. Complete physical examination will be performed at Screening, Day 1 of Cycle 2, 4, 6, at the 30 days (± 7 days) End of Treatment Follow-up Visit, and as determined by the Investigator, particularly to follow physical findings to resolution. Targeted physical exams should be conducted at any time to follow up on AE reports.

d. Height is only required to be recorded at Screening. Weight is to be recorded Cycle 1, Days 1 and 15, and on Day 1 of subsequent cycles and at the End of Treatment Follow-up Visits.

e. Vital signs include pulse, blood pressure, respiration rate, and temperature in the sitting position. Measure prior to dose and after completion of the IV infusion at the following time points: 5 minutes (± 5 minutes), 15 minutes (± 5 minutes), 30 minutes (± 5 minutes), and 1 hour (± 5 minutes) post-dose.

f. Screening labs to include the Quantiferon test (for latent TB), and all women of childbearing potential (including those who have had a tubal ligation < 6 months of first dose of FPA008) will have a serum pregnancy test.

g. **Clinical Safety Labs (**Table 7):

Hematology including CBC with differential, platelets, hemoglobin, hematocrit, RBC, and RBC indices.

Chemistry includes CK (creatine kinase), AST (aspartate transaminase), ALT (alanine transaminase), troponins (cardiac and skeletal), CK isoenzymes (if CK abnormal), carbon dioxide, bilirubin (direct and total), BUN (blood urea nitrogen), calcium, chloride, creatinine, glucose, LDH (lactate dehydrogenase), phosphate, potassium, sodium, magnesium, albumin, alkaline phosphatase, total protein, and uric acid. Additional tests may be obtained at any time, if clinically indicated. Total cholesterol will only be done at Screening and may be repeated at any time if clinically indicated.

Urinalysis will only be done at Screening and at the End of Treatment Follow-up Visits, and may be repeated at any time if clinically indicated.

Coagulation including INR, PT, and APTT.

h. Obtain ECG records at Screening, approximately 30 minutes post-dose on Day 15 for all cycles, and at the 30 days (± 7 days) End of Treatment Follow-up Visit. Additional ECGs should be obtained at any time, and/or if serum CK or cardiac troponin is elevated; if abnormal (excluding sinus tachycardia), ECGs should be obtained (if clinically indicated), until the abnormality is resolved or clinically stable. ECGs for each patient should be obtained from the same machine whenever possible. To minimize variability, it is important that patients be in a resting position for approximately ≥ 5 minutes prior to each ECG evaluation. Body position should be consistently maintained for each ECG evaluation to prevent changes in heart rate. Environmental distractions (e.g., television, radio, conversation) should be avoided during the pre-ECG resting period and during ECG recording.

i. MRI of the affected joint(s) will be performed during Screening and within 7 days of the following: 4 (C2D1), 8 (C3D1), and 16 (C5D1) weeks. Patients should have an MRI done at the 30 days (± 7 days) and 90 days (± 7 days) End of Treatment Follow-up Visits, unless it was already performed within the previous 6 weeks or if tumor progression was previously determined. Patients who have not progressed and enter Long-Term Follow-up should have MRI performed every 14 weeks (±2 weeks) for duration of response until progression, the patient undergoes local therapy (e.g., resection, radiation) or a new systemic therapy is initiated, for up to 52 weeks following C1D1. Response per MRI will be assessed using RECIST 1.1 and TVS based on independent central radiology review.

j. All women of childbearing potential (including those who have had a tubal ligation < 6 months of first dose of FPA008) will have a serum pregnancy test at Screening and at End of Treatment Follow-up Visits.

k. The Ogilvie-Harris, Brief Pain Inventory, and Joint Stiffness Numeric Rating Scale assessments will be performed at Screening, C1D15 (pre-dose), C2D1 (pre-dose), and then on Day 1 (pre-dose) for all subsequent cycles through 24 weeks of treatment, or until treatment is discontinued. These can be omitted if performed within 6 weeks prior to the End of Treatment Follow-up Visits. Patients who have not progressed and enter Long-Term Follow-up are to be followed every 14 weeks (± 2 weeks) until progression, the patient undergoes local therapy (e.g., resection, radiation) or a new systemic therapy is initiated, for up to 52 weeks following C1D1.

l. Optional archival tumor tissue will be collected at Screening, if available.

m. Optional synovial biopsies will be collected at Screening and up to -2 days prior to the C2D1 dose administration.

n. Optional synovial fluid aspirate will be extracted at Screening and up to -2 days prior to the C2D1 dose administration.

o. Blood samples will be collected for PK, ADA, and PD. Refer to Appendix 2 for collection times.

p. Whole blood will be collected and shipped overnight to the testing facility for analysis of $CD14^{+}/16^{+}$ monocytes. Refer to Appendix 2 for collection times.

q. ANA testing will be performed at Screening and at the 30 days (± 7 days) End of Treatment Follow-up Visit.

r. FPA008 study drug will be administered every 2 weeks (± 3 days) in 28-day cycles for 24 weeks of treatment. The Cycle 2, Day 1 infusion of FPA008 can only be administered after completion of the 28-day DLT window. All subsequent infusions can be administered with a ±3 day window. Patients should not have 2 doses of FPA008 within 7 days. The first dose of each cycle is considered Day 1 of each cycle, cycles will repeat every 28 days unless there is a treatment delay. Patients can have treatment delay of Day 1 of the subsequent cycle as long as the Day 1 treatment is within 6 weeks of the last treatment. FPA008 will be administered over approximately 30 minutes (± 5 minutes).

s. Performed at 30 days (± 7 days), 60 days (± 7 days) and 90 days (±7 days) after the last dose of study treatment for all patients who complete the treatment period or who terminate early. All adverse events (including serious adverse events), regardless of attribution, will be recorded until 90 days after the last dose of study treatment. Ongoing adverse events will be followed until the event has resolved to baseline grade, the event is assessed by the Investigator as stable, there is a satisfactory explanation for the changes observed, the patient is lost to follow-up, or the patient withdraws consent.

t. Patients who have not progressed should continue onto Long-Term Follow-up after completing the End-of-Treatment Follow-up Period. Patients are to be followed every 14 weeks (± 2 weeks) until progression, the patient undergoes local therapy (e.g., resection, radiation) or a new systemic therapy is initiated, for up to 52 weeks following C1D1.

u. Only ongoing adverse events thought to be related to study treatment should be followed during the Long-Term Follow-up Period.

v. Only local therapy (e.g., resection, radiation) or a new systemic therapy will be recorded during the Long-Term Follow-up Period.

w. PET scans will be performed in a subset of approximately 10 patients at Screening, Cycle 3 Day 1 (±7 days), C6D15 (±7 days) Visit, 90 days (±7 days) End of Treatment Follow-up Visit, and at the first Long-Term Follow-up Visit (14 weeks (± 2 weeks) post 90 days End of Treatment Visit).

Appendix 2: Study Flowchart for Pharmacokinetic, Immunogenicity, and Pharmacodynamic Blood Sample Collections

Study Cycle	Study Day	Time Point	Type of Sample
Cycle 1	Day 1 (First Dose)	≤ 4 hours Prior to infusion	FPA008 PK (serum)
			ADA (serum)
			Serum Biomarkers (serum)
			[redacted]
		15 minutes after end of infusion (±5 minutes)	FPA008 PK (serum)
			Serum Biomarkers (serum)
		4 hours after end of infusion (±5 minutes)	FPA008 PK (serum)
			Serum Biomarkers (serum)
			[redacted]
	Day 2	24 hours after infusion (±2 hours)	FPA008 PK (serum)
			Serum Biomarkers (serum)
			[redacted]
	Day 8	168 hours after infusion (±24 hours)	FPA008 PK (serum)
			Serum Biomarkers (serum)
			[redacted]
	Day 15 (Second Dose)	≤ 4 hours Prior to infusion	FPA008 PK (serum)
			ADA (serum)
			Serum Biomarkers (serum)
			[redacted]
		15 minutes after end of infusion (±5 minutes)	FPA008 PK (serum)
Cycle 2	Day 1 (First Dose)	≤ 4 hours Prior to infusion	FPA008 PK (serum)
			ADA (serum)
			Serum Biomarkers (serum)
			[redacted]
Cycle 3, and 5*	Day 1 (First Dose)	≤ 4 hours Prior to infusion	FPA008 PK (serum)
			ADA (serum)
			Serum Biomarkers (serum)
			[redacted]
		15 minutes after end of infusion (±5 minutes)	FPA008 PK (serum)
End of Treatment Follow-up and Long-Term Follow-up	At Visit	At Visit	FPA008 PK (serum)
			ADA (serum)
			Serum Biomarkers (serum)
			[redacted]

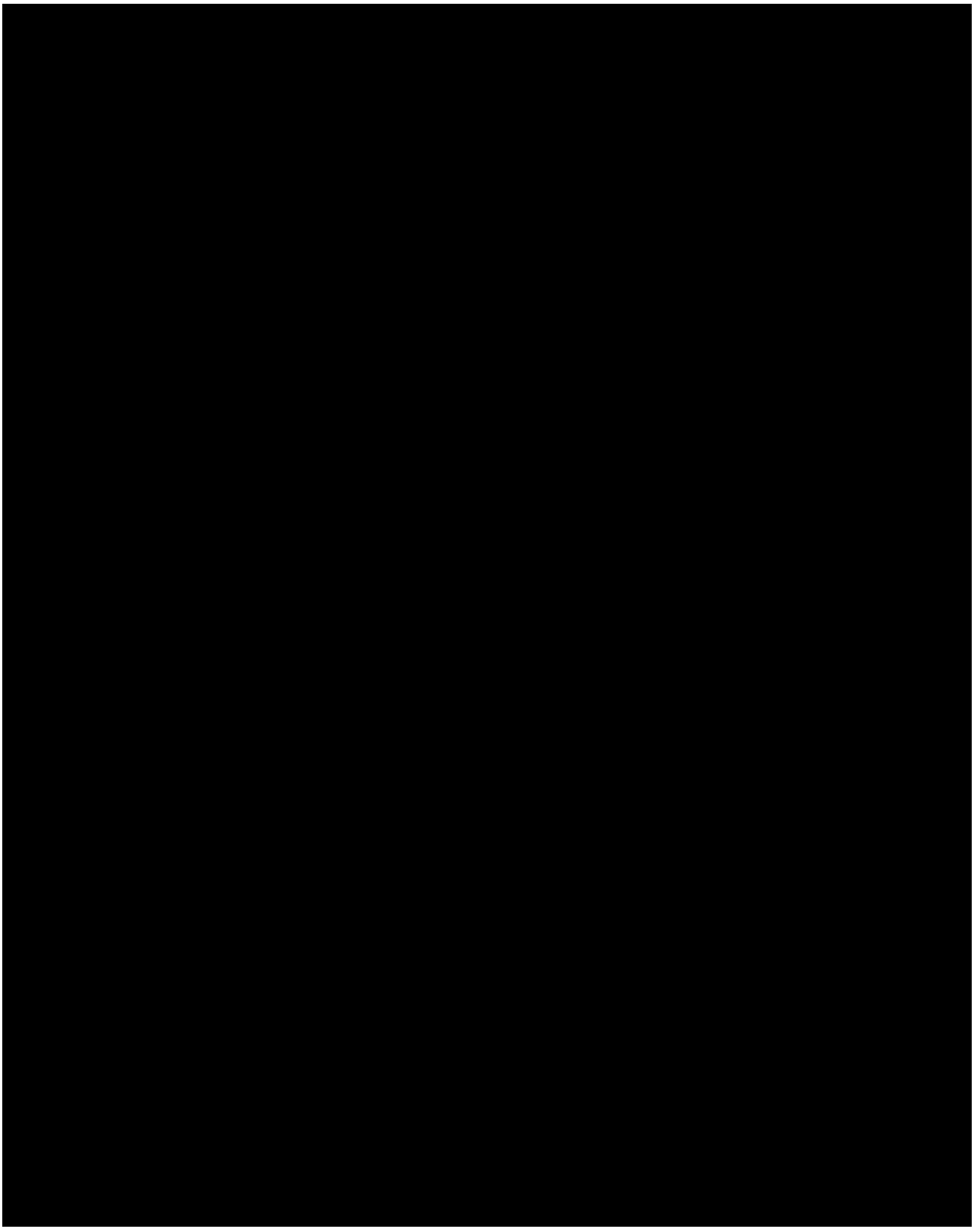
*The 15-minute post infusion PK blood draw is not required if FPA008 is not administered.

Appendix 3: ECOG Performance Status

Grade	Performance Status Criteria
0	Fully active, able to carry on all pre-disease activities without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light sedentary nature (light housework, office work).
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.

Appendix 4: Ogilvie-Harris Score for PVNS

Appendix 5: Brief Pain Inventory (Cleeland 1994)



Appendix 5: Brief Pain Inventory (contd.)

[redacted]

Appendix 6: Joint Stiffness Numeric Rating Scale

Appendix 7: Management of Systemic Hypersensitivity Reactions

Staff administering study drug are required to closely monitor all patients for possible systemic hypersensitivity reactions (e.g., generalized exanthema, urticaria, paraesthesia, bronchoconstriction, palpitations) over the first 180 minutes after infusion, paying particular attention to those patients with a history of asthma or systemic reactions to allergenic injections.

All systemic hypersensitivity manifestations will be captured on the appropriate eCRF page(s) and identified as being due to a hypersensitivity reaction.

Systemic hypersensitivity reactions will be managed according to treatment protocols in effect at the investigational site. In the absence of such a protocol, the following standardized treatment protocol will be used:

- Clinically mild reactions (e.g., generalized rash or itching, hives) are treated as soon as possible with Benadryl® (diphenhydramine hydrochloride) 25 to 50 mg, orally or IV at the Investigator's discretion. The period of observation is extended beyond 3 hours, as necessary, until symptoms and signs have resolved or stabilized. Patients who have experienced a clinically mild reaction may continue to have study drug administered.
- Clinically moderate reactions (e.g., hypotension, shortness of breath, facial edema) are treated immediately and supportive care measures instituted as medically indicated (e.g., IV fluids, corticosteroids, vasopressors, oxygen, bronchodilators, diphenhydramine, and acetaminophen). Vital signs are monitored at 10-minute intervals until they have normalized. The period of observation is extended beyond 3 hours, if necessary, until symptoms and signs have resolved. In the event of a clinically moderate reaction, the patient should receive no further treatment with study drug.
- Clinically severe reactions (e.g., marked hypotension, syncope, severe bronchoconstriction, tongue or throat swelling, significant angioedema) are treated immediately, under the direct supervision of the investigator, and supportive care measures instituted as medically indicated (e.g., IV fluids, corticosteroids, vasopressors, oxygen, bronchodilators, diphenhydramine, and acetaminophen). Vital signs and systems are monitored at a minimum of 10-minute intervals for as long as the investigator considers it necessary to ensure patient safety. In the event of a clinically severe reaction, the patient should receive no further treatment with study drug.

These clinical classifications are for the purpose of recommending treatment for patients who experience systemic hypersensitivity reactions. These classifications will not be used to grade the severity of the systemic hypersensitivity event within the eCRF. The severity of these events will be documented per the grading system presented in NCI CTCAE v4.03.