Statistical Analysis Plan

Protocol FPA008-002

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)

Statistical Analysis Plan
(SAP)

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Statistical Analyses Plan Approval Form

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This Statistical Analysis Plan has been approved by Five Prime Therapeutics, Inc. The following signatures document this approval.

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LIST OF ABBREVIATIONS

Abbreviation or special term	Explanation
ADA	Anti-drug antibodies
AE	Adverse Event
AI_Cmax	Cmax accumulation index; ratio of Cmax from any cycles to Cmax after the first dose
AI_Ctrough	Ctough accumulation index; ratio of Ctrough from any cycles to Ctrough after the first dose
AUC	Area under serum concentration-time curve
AUC(INF)	Area under serum concentration-time curve from time zero extrapolated to infinity
AUC(0-T)	Area under the serum concentration-time curve from time zero to time of last quantifiable concentration
AUC(TAU)	Area under the serum concentration-time curve in one dosing interval
CI	Confidence interval
C_{max}	Maximum observed serum concentration
C_{min}	Minimum observed serum concentration during a dosing interval (excludes pre-dose concentration before the first dose)
Ctrough	Concentration associated with the sample at the end of each dose interval
CL	Total body clearance
CR	Complete response
CSF1	Colony stimulating factor-1
CTx	Collagen-type I C-terminal telopeptide
CTCAE	Common Terminology Criteria for Adverse Events
CV	Coefficient of variation
DLT	Dose-limiting toxicity
dt-TGCT	Diffuse type tenosynovial giant cell tumor
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
IHC	Immunohistochemistry
IL 34	Interleukin 34
ISH	In Situ Hybridization
ITT	Intent-to-treat

Abbreviation or special term	Explanation
MedDRA	Medical Dictionary for Regulatory Activities
MRT	Mean residence time
MTD	Maximum tolerated dose
NCA	Non-compartmental analysis
NCI	National Cancer Institute
ORR	Objective response rate
PD	Pharmacodynamic
PD	Progressive disease
PK	Pharmacokinetic
PR	Partial response
PVNS	Pigmented villonodular synovitis
RD	Recommended dose
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	Serious adverse event
SD	Stable disease
STD	Standard deviation
TRAP5b	Tartrate resistant acid phosphatase 5b
t1/2	Terminal half-life
V_{ss}	Volume of distribution at steady state

1. INTRODUCTION

FPA008 is a humanized IgG4 monoclonal antibody with a single amino acid substitution in the hinge region to prevent hemi-dimer exchange. FPA008 has high affinity binding to human colony stimulating factor 1 receptor (CSF1R), a receptor tyrosine kinase.

2. STUDY OBJECTIVES

2.1. Primary Objectives

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

2.2. Secondary Objectives for Phase 1 and Phase 2

1. To characterize the safety and tolerability of cabiralizumab in patients with PVNS/dt-TGCT.
2. To determine the duration of response in responding patients.
3. To assess the pharmacokinetics (PK) of cabiralizumab in patients with PVNS/dt-TGCT.

2.3. Exploratory Objectives for Phase 1 and Phase 2

1. [redacted]
3. To evaluate synovial fluid for cabiralizumab concentration and changes in cellularity in selected patients.
4. To assess the use of analgesic medications prior to, and during the study
5. To assess functional outcomes as measured by
    - Ogilvie-Harris score developed specifically for PVNS (Appendix 6 in protocol).
    - Brief Pain Inventory (Appendix 7 in protocol)
    - Joint Stiffness Numeric Rating Scale (Appendix 8 in protocol)
    - EQ-5D-5L (Appendix 9 in protocol)
    - Global Impression Scales (Appendix 10 in protocol):
    - Patient Global Impression of Symptom Severity (PGIS)
    - Patient Global Impression of Treatment Satisfaction (PGITS)
    - Patient Global Impression of Treatment Side Effects (PGITSE)

- Clinician Global Impression of Severity – PVNS/dt-TGCT
- Pigmented villonodular synovitis signs and symptoms assessment form (PVNS-SSAF) (Appendix 11 in protocol)
- Patient Reported Outcomes Measurement Information System-Physical Function (PROMIS-PF) 10b (Appendix 12 in protocol)

3. STUDY DESIGN

3.1. General Study Design and Plan

This is a Phase 1/2 study. Phase 1 is a dose escalation, open-label, safety, tolerability, PK, and PD study of cabiralizumab.

Patients enrolled in Phase 1 and Cohort 2A will be treated in 28-day cycles. Each cycle will consist of two doses: on Day 1 and Day 15.

Phase 2 is a dose expansion, open-label, efficacy study of cabiralizumab. Phase 2 consists of two parts:

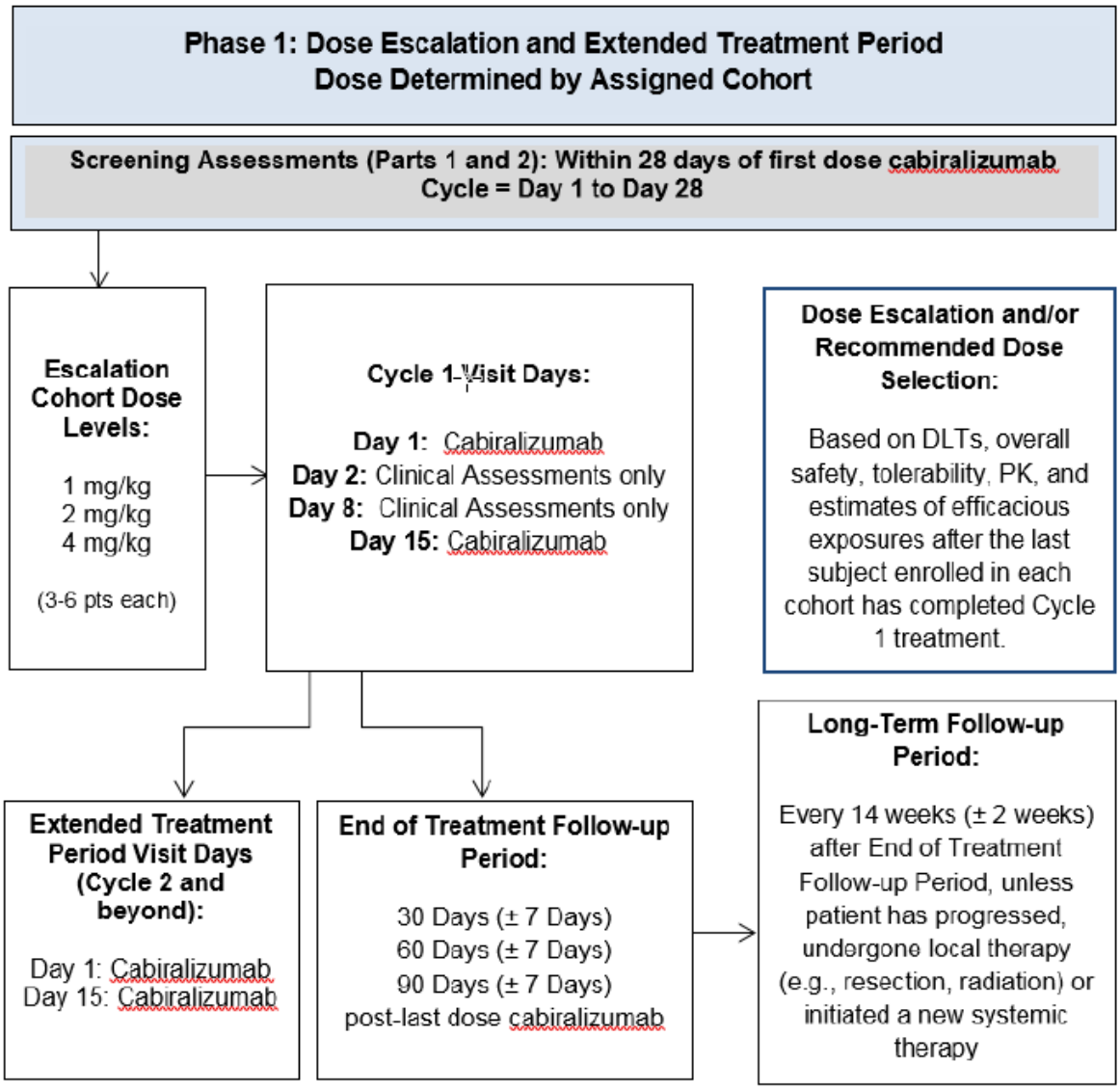
• Cohort 2A – 4 mg/kg Q2W
• Cohort 2B – 4 mg/kg on day 1 and 15, then Q4W thereafter.

3.2. Treatment Assignment

3.2.1. Phase 1 (Dose Escalation)

Dose escalation will continue until either the MTD or maximum feasible dose is reached, with a minimum of three patients enrolled in each cohort. The 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

Below is the study schema for Phase 1.



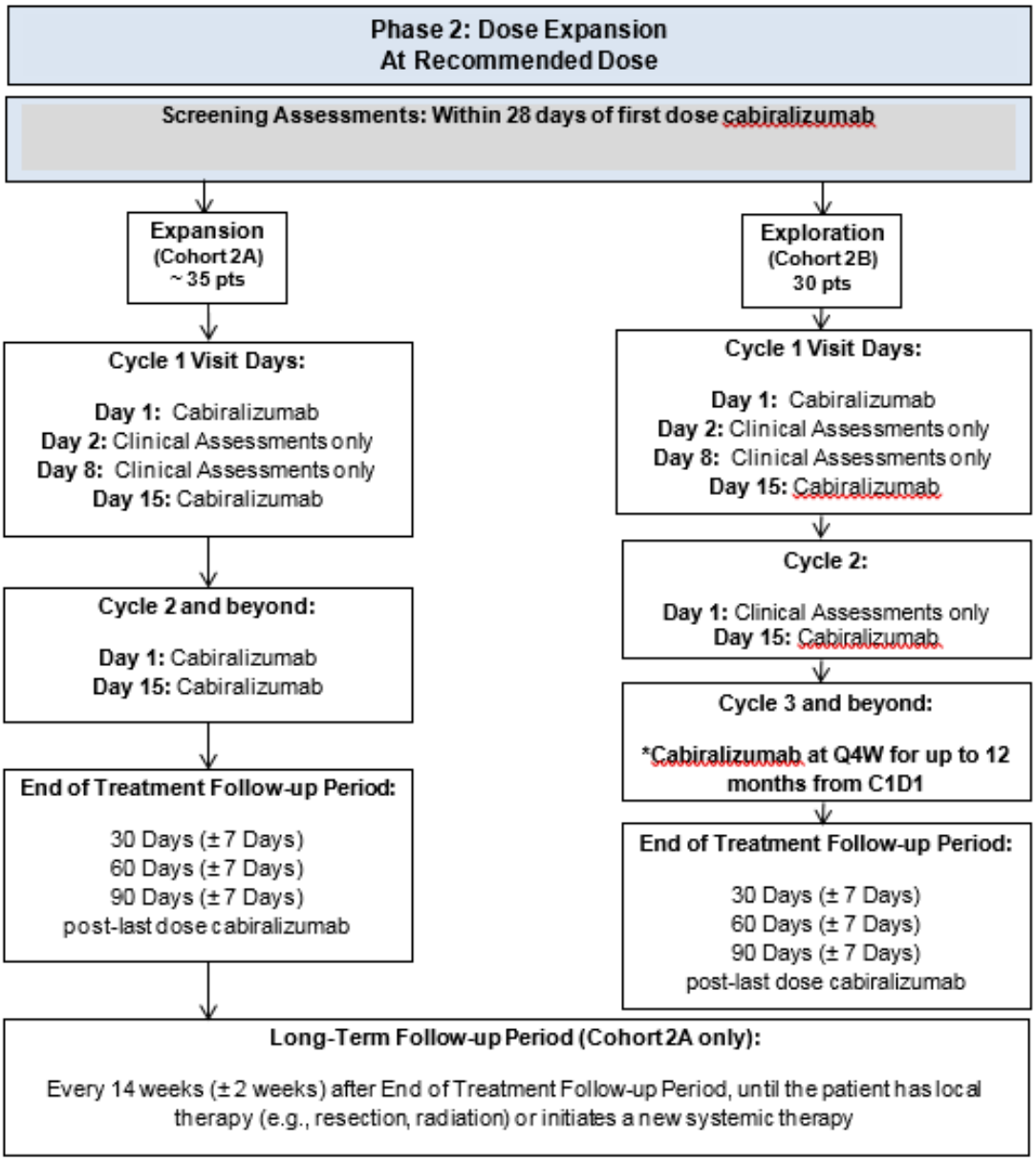
3.2.2. Phase 2 (Dose Expansion)

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.

Approximately 30 patients in Cohort 2A will receive treatment at the RD (determined to be 4 mg/kg every two weeks) for up to 12 doses or until disease progression. Additionally, up to five patients from Phase 1 may be retreated at the RD. Two retreatment patients have been treated as part of Cohort 2A. Cohort 2A is now closed for further enrollment. 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.

Approximately 30 patients will be enrolled. Patients in this cohort will receive 4 mg/kg cabiralizumab on Cycle 1 Day 1 and Cycle 1 Day 15, then every four weeks thereafter. Based on the response to treatment (including clinical benefit and tolerability), patients may have the dose level and frequency modified, following the guidelines outlined in Protocol Table 6. No dose regimen change is allowed before Cycle 2 Day 15 (except in cases of dose holds due to safety reasons).

Below is the study schema for Phase 2.



* Dose frequency can be reduced to Q6W or dose level can be reduced to 2 mg Q4W in subjects that do not tolerate 4 mg Q4W and can be increased to 4 mg to Q3W in subjects that tolerate well but do not experience clinical benefit. Dose titration will be based on Investigator judgment and after discussion with Sponsor

Visit schedule and assessment plan can be found in protocol Appendix 1 and 2.

3.3. Sample Size Consideration

3.3.1. Phase 1 (Dose Escalation)

Three patients per dose group, with a sample size increased to six 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 one of three patients, then three additional patients will be enrolled at that same dose level. Dose escalation will continue until two of three to six 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 cabiralizumab. It is anticipated that 12-15 patients may be enrolled in Phase 1.

3.3.2. Phase 2 (Dose Expansion)

For the objective of estimating the ORR of cabiralizumab in patients with PVNS/dt-TGCT, it is estimated that approximately 30 naïve patients will be enrolled in Cohort 2A of Phase 2. With sample size of 30, it will allow to exclude 19% when the observed ORR is 33% or higher. Additionally, up to five patients from Phase 1 will be enrolled into Cohort 2A. This is to gain more information about the safety and activity of cabiralizumab in selected patient populations and the data from these cohorts may be used to inform future clinical studies in this patient population. A total of approximately 65 patients will be enrolled at the RD overall. Table 1 displays the corresponding two-sided 95% CI and the precision for various sample sizes and observed response rates (Agresti 1998).

Table 1. Two-Sided 95% CIs of the Observed Response Rate

Sample Size	Observed Response Rate	95% CI	Precision (longest one-sided CI length*)
30	10/30 (33%)	19% to 50%	~17%
	11/30 (37%)	22% to 53%	~16%
25	8/25 (32%)	17% to 50%	~18%
	9/25 (36%)	20% to 54%	~18%
20	7/20 (35%)	18% to 56%	~21%
	8.10.1. 8/20 (40%)	8.10.2. 22% to 61%	~21%

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

4. ANALYSIS POPULATIONS

Below is a description of the Analysis Sets defined for this study.

4.1. Safety Population

All patients who have received any portion of at least one dose of cabiralizumab

4.2. DLT-Evaluable Population

All patients enrolled into Phase 1 of the study who received at least 2 doses of cabiralizumab and completed Cycle 1 of treatment, or who experienced a Dose-limiting toxicity (DLT) in Cycle 1.

4.3. Efficacy-Evaluable Population

All patients who met eligibility criteria received at least 1 dose of cabiralizumab, have measurable tumor lesions at baseline, and have at least 1 post-baseline disease assessment. Efficacy will be analyzed for all patients enrolled and separately for Phase 1 and Phase 2.

The efficacy-evaluable population used for analysis of TVS will be based on the assessments by TVS. Others will be based on the assessments by RECIST v1.1.

4.4. Intent-to-Treat (ITT) Population

All treated patients. Patient without post-baseline disease assessment will be considered as non-responder.

4.5. PK Populations

PK Concentration Population: All subjects who receive at least one dose of cabiralizumab and have at least one available serum concentration data.

PK Evaluable Population: Subjects in the PK Concentration Population who have adequate PK assessments to reliably derive at least one PK parameter. This is the population of primary interest for the summaries of the PK parameters and exploratory analyses of the association of PK data with efficacy measures.

4.6. ADA-Evaluable Population

All subjects who received at least one dose of cabiralizumab and have at least one available ADA data.

5. GENERAL STATISTICAL CONSIDERATIONS

5.1. General Principles

The statistical analysis will be conducted following the principles specified in the International Conference on Harmonisation (ICH) Topic E9 Statistical Principles for Clinical Trials (CPMP/ICH/363/96).

The statistical analysis will be performed using SAS® version 9.3 (SAS Institute, Inc.) or later.

In general, all analyses will be descriptive and will be presented by phase and overall as below.

- Phase 1
    - 1 mg/kg
    - 2 mg/kg
    - 4 mg/kg
    - Phase 1 Total
- Phase 2
    - Cohort 2A
    - Cohort 2B
    - Phase 2 Total
- Overall Total

Phase 1 patients dosed at the re-treatment in Phase 2 Cohort 2A will be summarized in both initial Phase 1 group and Cohort 2A. In the initial Phase 1 column, subjects will be summarized before re-treatment. The baseline is the latest observation before 1st dose of study treatment. The re-treated subjects in Cohort 2A will be summarized on/after re-treatment. The baseline is the latest observation before 1st dose of re-treatment.

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. Confident intervals (CI) may be included as appropriate.

Patient data listings will be based on all enrolled patients, unless specified otherwise and will be sorted by Patient Identifier and Visit. Study day relative to first dose of study drug may be presented. Study day relative to first dose will be calculated as: event date – first dose date in the study (+ 1 if event date ≥ first dose date in the study).

When appropriate, baseline is defined as the last non-missing result with a collection date-time less than the date-time of the first dose of study medication.

PK analyses will be presented by individual cohort for each phase.

5.2. Handling Dropouts and Missing Data

Missing values in the efficacy data will be treated as missing; no efficacy data will be imputed. Mixed effect Model Repeat Measurement (MMRM) approach will be used when applicable.

Imputation of partial dates will be made for AE onset and stop dates, start and end dates of prior/concomitant medication, start date of subsequent anticancer therapy, date of initial diagnosis and death date. No imputation will be made if dates are completely missing or year is missing. See Section 7.2 for detailed imputation rules for missing data.

5.3. Interim Analyses and Unblinding

There is no interim analysis planned for this study.

Safety data will be reviewed on a routine basis. 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.

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

6. STATISTICAL ANALYSIS

6.1. Subject Information

6.1.1. Subject Disposition

The number and percentage of patients for each of the following will be provided by phase and overall.

- Patients enrolled
- Patients who received study treatment
- Patients who did not receive study treatment
- Patients discontinued from treatment, overall and by reason
- Patients who completed the study
- Patients discontinued from study, overall and by reason
- Analysis populations

Listings will be provided for discontinued patients and patients completing the study. The summaries and listing will be based on All Enrolled patients.

6.1.2. Protocol Deviations

A summary of the number and percentage of patients with protocol deviations by type of deviation will be provided by phase and overall. All protocol deviations felt to be significant enough to impact the interpretation of the results will be presented in the data listings.

Possible protocol deviations will include but are not limited to:

- Violations of eligible criteria
- Disallowed medications or procedures
- Issues regarding informed consent form

6.1.3. Study Treatment

Descriptive statistics will be provided by phase and treatment for the following

- Cumulative dose (mL)
- Average dose (mL)
- Duration of therapy (days)
  Duration of therapy is defined as the number of days between start date of first dose of study treatment and stop date of last dose of study treatment + 1.
- Compliance (%)
  Compliance is defined as the sum of all doses administered across the treatment phase and divided by the planned dose for the patient for phase.
- Dose intensity (%)
  Dose intensity is defined as actual total dosage / planned total dosage. The planned total dosage is derived based on 6 cycles of treatments at the assigned dose level for discontinued patients. For study completers and for the ongoing patients, the planned total dosage is determined by the # of planned dosing visit*assigned dose level*weight.
- Dose modifications
- Dose reduction
- Dose interruption

6.1.4. Demographics and Baseline Characteristics

Demographic data, medical history, other baseline characteristics, concomitant disease, and concomitant medication will be summarized by phase and overall in the Safety population.

6.1.4.1. Demographics

- Age (continuous)
- Sex (Mail, Female)
- Race
- Ethnic group

6.1.4.2. Baseline characteristics

- Height (cm)
- Weight (kg)
- Synovium Biopsy - Affected Body Part / Joint
- Synovium Fluid - Affected Body Part / Joint
- ECOG Performance Status
- Baseline Ogilvie/Harris Score for PVNS (continuous)
    - Total Score
    - Pain
    - Synovitis/Effusion
    - Range of Motion
    - Functional Capacity

6.1.5. Medical History and Concomitant Diseases

Medical history and concomitant diseases will be coded using MedDRA 18.0, sorted alphabetically by system organ class and preferred term, summarized by phase and overall for the safety population.

6.1.6. Concomitant Medications

Medications, coded using WHO Drug version March 2015 into drug class (ATC level) and preferred term, will be summarized. The summary of concomitant medications will show the number and percentage of patients taking concomitant medications by ATC Level 1 (Body System) and preferred drug name.

In the summary of concomitant medications, each patient is counted once within each preferred drug name and ATC Level 1 (Body System).

The table will be presented by phase and overall. All medications will be sorted by descending total for ATC Level 1 (Body System) then descending total for preferred drug name frequency.

6.2. Efficacy Analysis

Patients will be classified according to their best objective tumor response (complete response [CR], partial response [PR], stable disease [SD], or progressive disease [PD]) per RECIST v1.1 by investigator assessment.

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].
Patients with a best objective tumor response of CR or PR with duration of at least four weeks (28 days) will be further classified as having a confirmed objective tumor response.

6.2.1. Primary Endpoint: Confirmed Objective Response Rate per RECIST v1.1

Response for each time point will be calculated using algorithms in Eisenhauer 2009, section 4.3 and Table 1. The best objective response will be calculated using the best response among visits that are prior to an event or censoring variable for response (i.e. end of treatment, progression, death, last evaluable assessment, new anti-cancer therapy, see variables for calculating DOR in Table 2 of section 6.2.2), using calculations in Eisenhauer, Section 4.4 and Table 3. The confirmed objective response of CR or PR will require confirmation by a supporting result at least 4 weeks after the visit that the response is first observed. Establishment of stable disease will require a minimum of 42 days from day or first dose of study drug.

The earliest date of progression based on radiographic evidence will be calculated from target lesions, non-target lesions, and new lesions at each visit (Eisenhauer 2009, section 4.3). The date of progression will be used for analyses of DOR, as well as to be used as one criterion establish the latest time that a best objective response can be established (in addition to time established by other event or censoring variables as described in section 6.2.2).

The primary efficacy endpoint is the incidence of Investigator-assessed, confirmed objective response rates (ORR) per RECIST v1.1 in Phase 2. Confirmed objective overall response rate (ORR) is defined as total number of subjects with confirmed objective responses of either CR or PR divided by the total number of subjects in each cohort.

The confirmed best objective response and ORR will be summarized with the frequency count and the percentage of subjects in each category. 2-sided 95% confidence interval for ORR will be provided by using Agresti (1998) approximate and exact method.

Analysis will be performed by phase and overall in Efficacy-Evaluable population.

6.2.2. Secondary Endpoint: Duration of Response (DoR)

DoR by RECIST v1.1 by investigator assessment will be calculated as the number of days from the first documentation of confirmed objective 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.

DoR for CR and PR patients will be summarized with descriptive statistics as well as categorically, whereas median and the associated confidence interval is to be estimated using Kaplan-Meier methodology. The detailed censoring rules are displayed in Table 2.

Table 2: Censoring Rules for DoR

Situation	Outcome	Date of Progression or Censoring	Event Description/ Censoring Reason
Disease progression before receiving Subsequent anticancer therapy or data cutoff, which ever happens first	Event	Date of death or first documented progression per RECIST 1.1, whichever is earlier (excludes clinical progression)	PD
Death without documented PD and not receiving new anticancer therapy on or before data cutoff	Event	Date of death or first documented progression per RECIST 1.1, whichever is earlier (excludes clinical progression)	Death
Subsequent anticancer therapy, tumor-directed radiotherapy, or tumor-directed surgery received without documented PD or death prior or on the same day	Censored	Date of last evaluable tumor assessment prior to the date of initiation of subsequent anticancer therapy	Subsequent anticancer therapy
No death, PD or subsequent anticancer therapy before data cutoff	Censored	Date of last evaluable assessment	Data cutoff
Discontinued from study without death, PD or subsequent anticancer therapy	Censored	Date of last evaluable assessment	Study discontinued

Analysis will be performed by phase and overall in Efficacy-Evaluable population.

6.2.3. Exploratory Endpoints:

6.2.3.1. ORR per RECIST v1.1 by Independent Central Review

The confirmed best overall response will be calculated using the same rule as described in Section 6.2.1.

Overall tumor assessment and confirmed best overall response by Independent Central Review will be listed only.

6.2.3.2. ORR by Tumor Volume Score (TVS)

The best overall response will be calculated using the best response among visits that are prior to an event or censoring variable for response (i.e. end of treatment, progression by TVS, death, last evaluable assessment, new anti-cancer therapy, see variables for calculating DOR in Table 2 of section 6.2.2)

Tumor volume score and confirmed best overall response per the Independent Central Radiology Review will be listed only.

6.2.3.3. Symptom and Functional Outcomes

The following symptoms and functional outcomes will be listed only.

- Ogilvie-Harris score developed specifically for PVNS (Cohort 2A only)
- Brief Pain Inventory (short form)
- Joint Stiffness Numeric Rating Scale
- EQ-5D-5L
- Global Impression Scales
- PVNS-SSAF
- PROMIS-PF 10b
- Range of motion by radiographic improvement

6.3. Safety Analysis

Safety analyses will be performed separately within both phases of the study and for all patients combined. Unless otherwise specified, all analyses will be performed using the Safety population. AEs, clinical laboratory information, vital signs, ECOG performance status, weight, ECGs, and concomitant medications/procedures will be tabulated and summarized. Safety summaries for clinical laboratory values, vital signs, and ECG will be presented by nominal visit.

6.3.1. Adverse Event

A treatment-emergent AE (TEAE) is defined as an AE that was present or worsened after 1st dose of study treatment. An AE that was present at treatment initiation but resolved and then reappeared and the event severity increase while the subject was on treatment is also a TEAE. A treatment related AE is an AE noted as related to cabiralizumab by the investigator or with a missing relationship.

All AEs will be coded to SOC and PT using Medical Dictionary for Regulatory Activities (MedDRA Version 18.0 or later). AEs are graded for severity by the investigator (or representative) using the National Cancer Institute Common Toxicity Criteria for Adverse Events (NCI-CTCAE) version 4.03.

Overall summary of any TEAEs and treatment-related TEAEs by worst CTC grade will be presented by SOC/PT. All recorded AEs occurring in the pre-treatment, on-treatment, and post-treatment period will be listed. The AE summaries will be presented by phase and overall for the Safety population.

Summary:

An overall summary of TEAEs will summarize the number (%) of patients with:

- at least one TEAE
- at least one treatment-related TEAE
- at least one grade 3 or higher TEAE
- at least one treatment-related grade 3 or higher TEAE
- AE leading to treatment discontinuation
- fatal TEAE
- treatment-related fatal TEAE
- at least one serious TEAE
- at least one treatment-related serious AE

Summaries of the following TEAEs will be provided by SOC/PT and worst CTC grade:

- All TEAEs
- AE leading to treatment discontinuation
- Serious TEAEs
- Treatment related serious AEs

Summaries of the following TEAEs will be provided by PT and worst CTC grade:

- All TEAEs
- TEAEs with Grade 3 or higher
- Treatment-related AEs

By-participant AE, SAE and AEs leading to discontinuation listings will be provided for the Safety population.

6.3.2. Deaths

All recorded deaths for All safety population will be listed.

6.3.3. Clinical Laboratory Evaluations

Observed and change from baseline of continuous clinical laboratory values (chemistry, hematology) for each parameter will be summarized for the maximum value, minimum value, and last available assessment will also be summarized.

All laboratory data will be listed by subject.

Urinalysis laboratory tests will be presented in data listing only.

All the laboratory summary tables will be presented by phase and overall for safety population.

6.3.3.1. Abnormal Hepatic Test

The number (%) of subjects with the following laboratory abnormalities from on-treatment evaluations will be summarized:

- Isolated total bilirubin > 2 to ≤ 3 x ULN
- Concurrent ALT or AST > 3 x ULN ***and*** Total bilirubin > 2 x ULN
- Concurrent ALT or AST > 5 to ≤12 x ULN ***and*** Total bilirubin ≤ 2 x ULN
- Concurrent ALT or AST > 12 to ≤ 20 x ULN ***and*** Total bilirubin ≤ 2 x ULN
- ALT or AST > 20 x ULN ***or*** Total bilirubin > 3 x ULN

A window of ± 3 days is applied to the concurrent abnormality. The days to onset is defined as the date abnormality criteria is first met - first dose date+1. For the concurrent abnormality, this date refers to the latter date when ALT or AST and Total bilirubin meets the abnormality criteria.

A by-subject listing of these specific abnormalities will be provided if needed.

6.3.4. Physical Examination

Results of physical examinations will be listed.

6.3.5. Vital Signs

Vital signs parameters like systolic blood pressure, diastolic blood pressure, pulse, respiration rate, and temperature will be summarized for absolute values of pre-infusion and post-

infusions and maximum change from pre-infusion at each scheduled visit by phase and overall for safety population. Supportive listing will be provided.

6.3.6. ECOG Performance Status

Eastern Cooperative Oncology Group (ECOG) performance status will be summarized categorically and descriptively at baseline, last assessment, minimum and maximum by phase and overall for the safety population. Supportive listing will be provided.

6.3.7. 12-Lead ECG

Observed values and change from baseline of 12-lead ECG parameters (HR and PR, RR, QRS, QT, QTc (QTcF, QTcB and other) intervals) will be summarized descriptively at baseline, last assessment, minimum and maximum change by phase and overall.

Supportive listing will be provided.

6.3.8. Pregnancy Testing

A listing of pregnancy tests results will be provided for all treated female subjects.

6.4. Pharmacokinetics

6.4.1. Serum cabiralizumab Concentration

Individual and mean serum concentration of cabiralizumab versus time data will be plotted by individual cohort and phase. Summary statistics will be tabulated for the serum concentration-time data of cabiralizumab, as appropriate. For the purpose of calculating or plotting mean concentration-time data, below the lower limit of assay quantitation (LLOQ) values will be treated as missing.

6.4.2. PK Parameters

The PK evaluable population will be used for all summaries of the PK parameters. Summary statistics will be tabulated for each PK parameter by individual cohort and phase. Geometric means and coefficients of variation will be presented for Cmax, AUC(0-T), AUC(TAU), Cmin, Ctrough, CL, Vss, MRT and AIs, as appropriate. Medians and ranges (minimum and maximum) only will be presented for Tmax. Means and standard deviations will be presented for other PK parameters (i.e., t1/2). Pharmacokinetic parameters of cabiralizumab will be derived from the serum concentration versus time profiles for the intensively sampled Cycle 1 Day 1 dose administration in both Phase 1 and Phase 2 of the study. Individual PK parameter values will be derived by non-compartmental methods by a validated PK analysis program using actual times.

Parameter	Units	Definition
Cmax	µg/mL	Maximum observed serum concentration
Tmax	h	Time of maximum observed serum concentration
AUC(INF)	µg.d/mL	Area under the serum concentration-time curve from time zero extrapolated to infinity
AUC(0-T)	µg.d/mL	Area under the serum concentration-time curve from time zero to time of last quantifiable concentration
AUC(TAU)	µg.d/mL	Area under the serum concentration-time curve in one dosing interval
Cmin	µg/mL	Minimum observed serum concentration during a dosing interval (excludes pre-dose concentration before the first dose)
Ctrough	µg/mL	Concentration associated with the sample at the end of each dose interval.
CL	L/d	Total body clearance calculated as Dose divided by AUC(INF) for Cycle 1, Day 1
AI_Cmax	-	Cmax accumulation index; ratio of Cmax from any cycles to Cmax after the first dose
AI_Ctrough	-	Ctough accumulation index; ratio of Ctrough from any cycles to Ctrough after the first dose
pAUCe	%	Percent of AUC extrapolated from the last quantifiable concentration to infinity (Cycle 1, Day 1 only)
λz	d^{-1}	Slope of terminal log-linear elimination phase
Adj R^2	-	Adjusted R^2 of terminal elimination phase
Lz_Start	d	The time point starting the log-linear elimination phase defining the terminal half-life
Lz_End	d	The time point ending the log-linear elimination phase defining the terminal half-life

Parameter	Units	Definition
Lz_N	-	Number of time points in the log-linear elimination phase defining the terminal half-life
MRT	d	Mean residence time. MRT = (AUMCinf/AUCinf) – T/2 where AUMCinf=Area under moments curve of the serum concentration-time from time 0 to infinity, AUCinf=Area under the serum concentration-time curve from time 0 to infinity, and T= infusion duration.
t1/2	d	Terminal half-life calculated post first dose. t1/2=ln(2)/λz
Vss	mL/kg	Steady-state distribution volume projected post first dose. Vss= CL*MRT.

Dose-normalized values for Cmax and Ctrough will also be presented using the actual dose administered.

6.4.3. Quality Control Methods for PK Data Analysis

The PK analysis will be subject to Quality Control (QC) review and also review by an independent pharmacokinetist at ICON.

6.4.4. Pharmacokinetic Assessments

6.4.4.1. PK analysis Software

The PK parameters will be calculated from the serum drug concentration-time data and actual elapsed sampling time using a non-compartmental analysis (NCA) method with i.v infusion input in Phoenix WinNonLin (Build 8.0.0.3176 or higher, Certara LP, St. Louis, MO). Alternative PK analysis methods may be considered if necessary, for example, a population PK analysis or compartmental modeling. Data summaries and plots will be produced using SAS Version 9.1 or higher (SAS Institute, Cary, NC).

6.4.4.2. PK Parameter Evaluation

PK parameters including Cmax, AUC, Cmin, Ctrough, CL, Vss, and MRT will be estimated. The cabiralizumab accumulation ratio for Cmax and Ctrough will be estimated for different cycles, as data permit.

Dose-proportionality will be assessed based on available cabiralizumab PK parameters if applicable.

Only data points that describe the terminal elimination log-linear decline will be used in the regression equation for calculation of λz. Cmax and any data point in the distribution phase

will not be included in the calculation of λz. A minimum of 3 points will be used for determination of the terminal elimination phase rate constant. A value of adjusted r^2 >0.80 will be considered acceptable for the calculation of the terminal elimination phase rate constant. If adjusted r^2 falls below 0.80, or the above conditions are not met, then the terminal elimination phase rate constant and the associated values of t1/2, AUC(INF), CL and Vss will be flagged. If pAUCe is more than 20%, then AUC(INF) and CL will be flagged. Flagged values will not be included in the calculation of descriptive statistics.

6.4.4.3. Treatment of Outliers

Individual serum concentration-time points, if considered anomalous, may be excluded from the analysis at the discretion of the pharmacokineticist following a review of the available documentation. Any such exclusion will be discussed with the Sponsor's Clinical Pharmacologist and clearly outlined in the CSR.

Entire individual treatment profiles for a subject may be excluded following review of the available documentation and discussion with the Sponsor. However, results of analysis with and without the excluded profiles may be presented in the CSR. Any such exclusion will be clearly listed in the CSR along with justification for exclusion.

Any anomalous concentration values observed prior to the first dose will be identified and discussed in the CSR.

6.4.4.4. Non-Quantifiable or LLOQ Concentrations

For the calculation of PK parameters, predose concentration values prior to the first quantifiable concentration that are below LLOQ values will be assigned a value of zero and thereafter any LLOQ values will be set to missing.

6.5. Immunogenicity

Defined as an immune response to cabiralizumab will be assessed by measurement of total anti-cabiralizumab antibodies from all subjects. Immunogenicity testing will consist of screening, confirmation, and titration for cabiralizumab. To classify the ADA status of a subject using data from an in vitro test method, each sample from a subject is categorized based on the following definitions:

Table 1. Sample ADA Status

Sample ADA Status	Definition
Baseline ADA-positive sample	ADA is detected in the last sample before initiation of treatment

Baseline ADA-negative sample	ADA is not detected in the last sample before initiation of treatment
Treatment Induced ADA-positive sample	1) an ADA detected (positive seroconversion) sample in a subject for whom ADA is not detected at baseline, or (2) an ADA detected sample with ADA titer to be at least *4*-fold or greater (≥) than baseline positive titer
Treatment ADA-negative sample	ADA sample that is not deemed ADA-positive

Next, using the sample ADA status, subject ADA status is defined as follows:

Table 1.1 Subject ADA Status

ADA Status	**Definition**
Baseline ADA-positive	A subject with baseline ADA-positive sample
Baseline ADA-negative	A subject with baseline ADA-negative sample
Treatment Induced ADA-positive	A subject with at least one ADA positive-sample relative to baseline at any time after initiation of treatment
Treatment ADA-negative	A subject with no ADA-positive sample after the initiation of treatment

6.6. Pharmacodynamics

PD analysis will not be included in the SAP

7. CONVENTIONS

7.1. Decimal Places

Decimal places originally recorded in the data will be displayed in the listings. In the summaries, values that are directly from the original value, such as Range (Minimum and Maximum) will be reported in the original significant decimal places. Values that are calculated directly from the original value such as Mean and Median are reported in the original significant decimal places + 1 more decimal place. Values that are calculated from calculated values such as standard deviation and standard error will be reported in the original significant decimal places + 2 more decimal places.

7.2. Missing Data

The general rules for imputation is:

- Use the 15th of the month, if only day is missing.
- Use June 30th, if month and day are missing.

If the imputed date for initial diagnosis is on or after date of the first dose, the date of first dose-1 will be used. If the imputed date for subsequent anti-cancer therapy is before the date of last dose, the date of last dose + 1 will be used.

If the imputed date is for an AE start date and is in the same year and month as but before the first dose date, then the first dose date will be used, or if the imputed AE start date is after the AE end date, then the AE end date will be used. If the imputed date for an AE start date is in the same year and month as but after the last dose date days, then the last dose date days will be used.

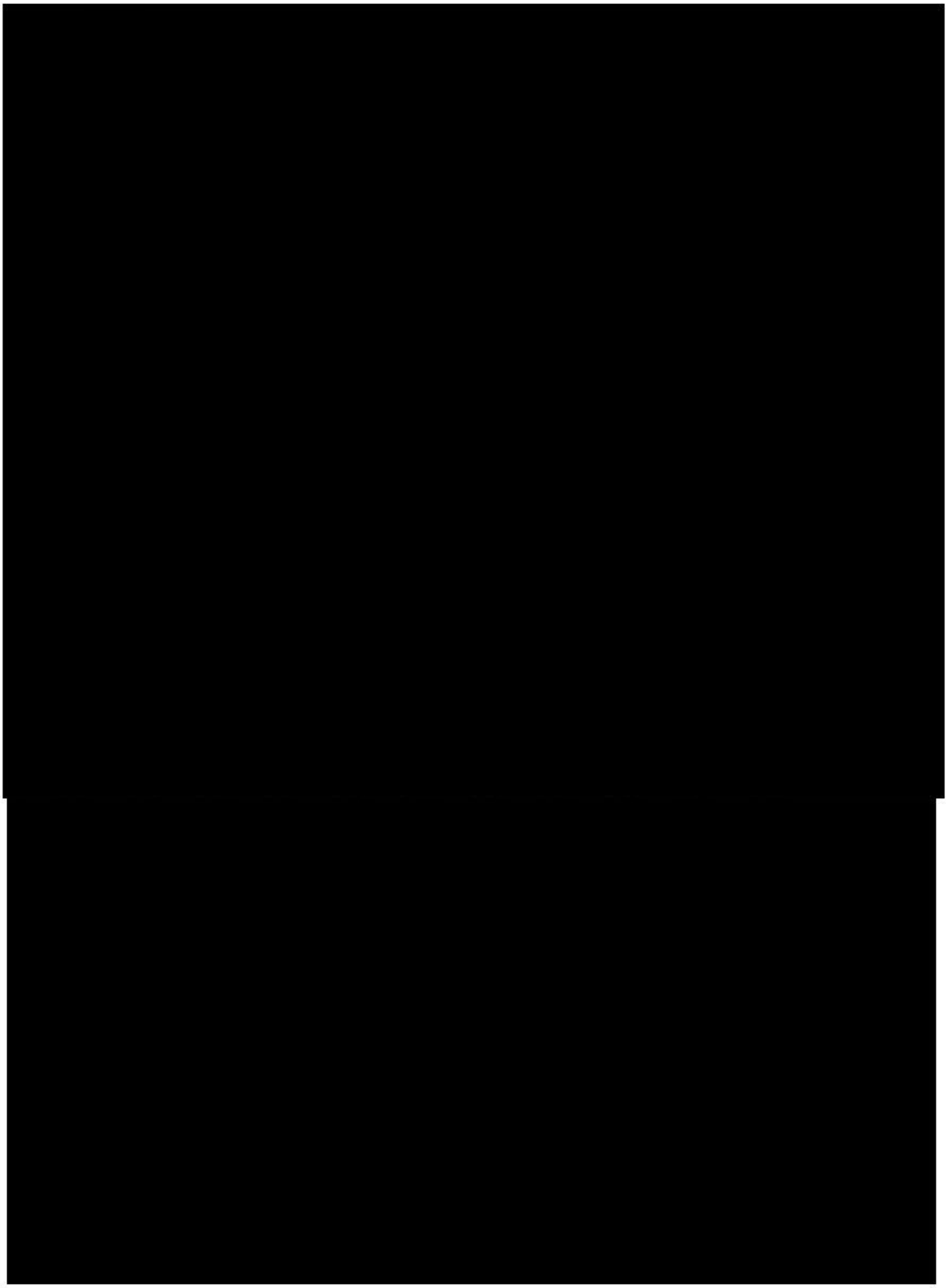
If the imputed date is for an AE end date and is after the death date, the date of death will be used, or if the imputed AE end date is before the AE start date, the AE start date will be used.

8. REFERENCES

9. APPENDICES

9.1. Ogilvie-Harris Score for PVNS

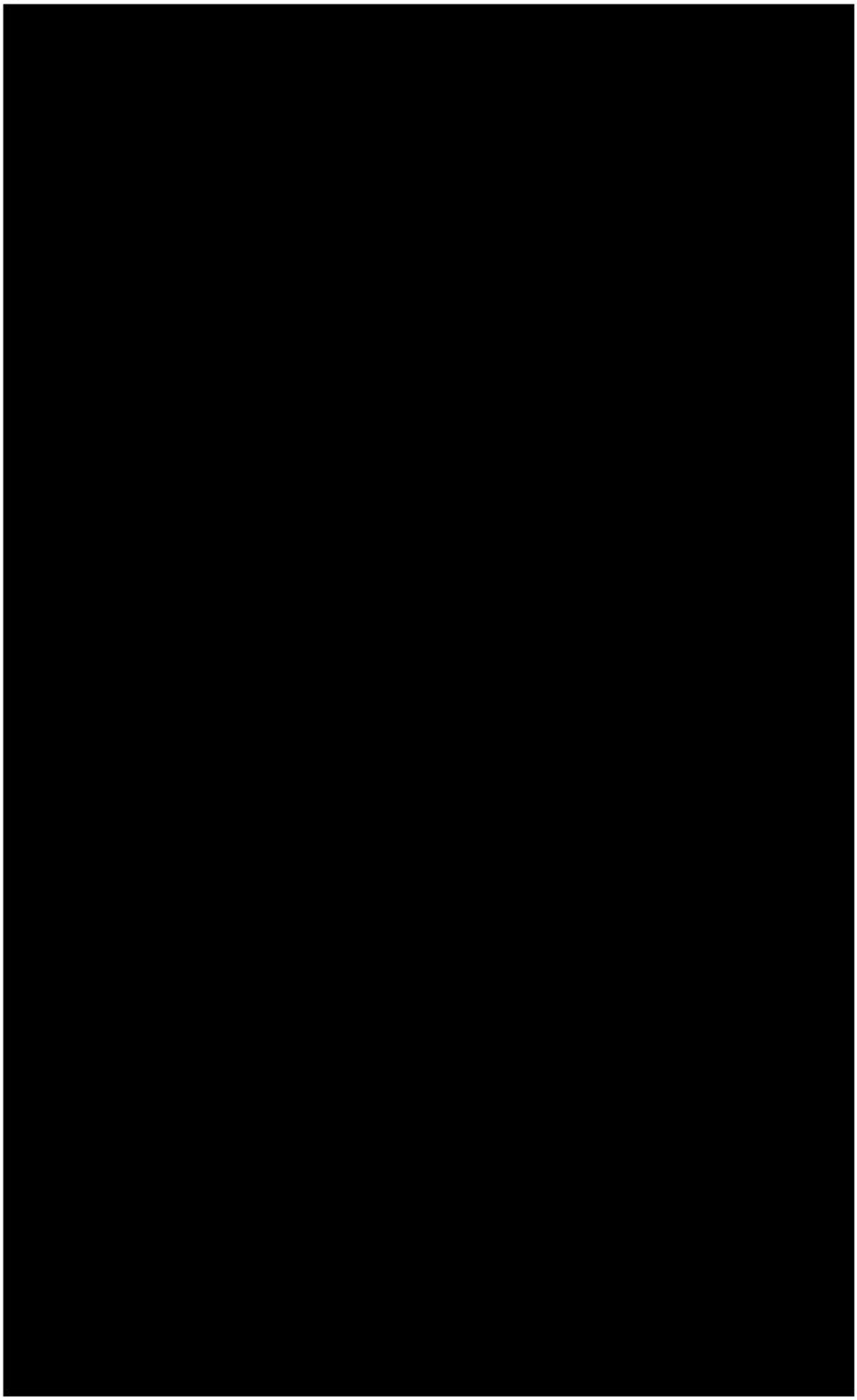
9.2. Brief Pain Inventory (short form)



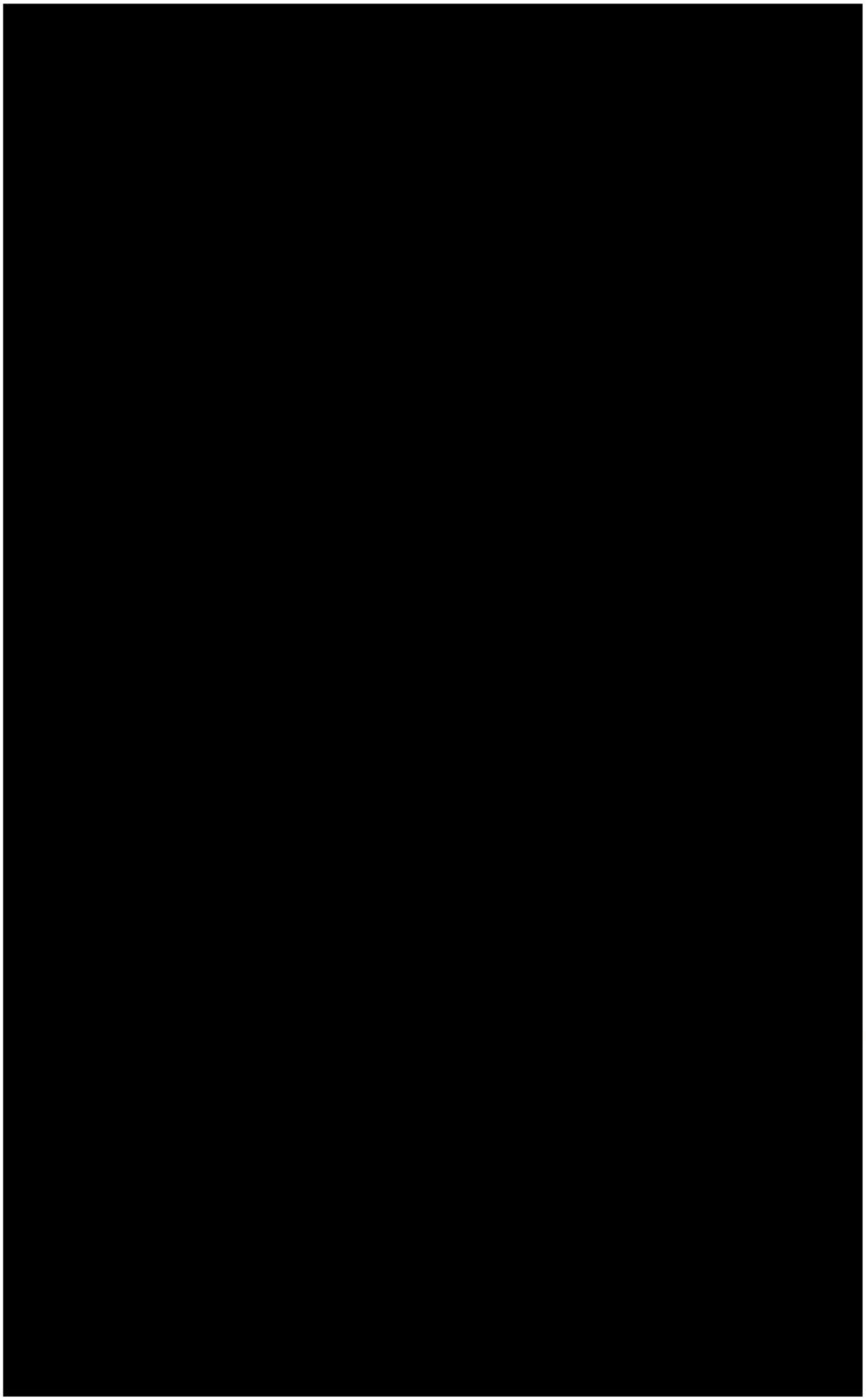
9.3. Joint Stiffness Numeric Rating Scale

9.4. EQ-5D-5L

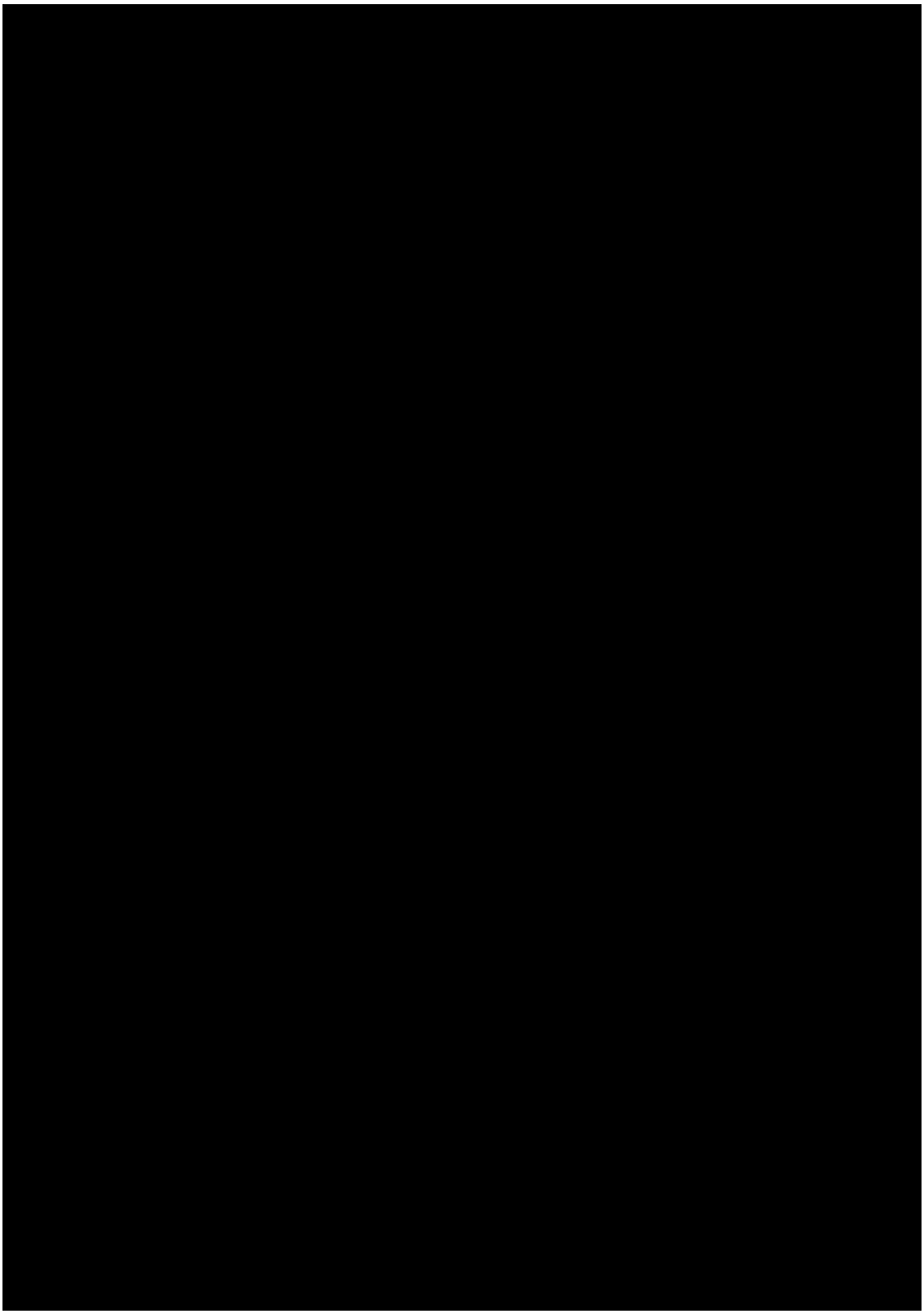
[redacted]



9.5. Global Impression Scales



9.6. PVNS-SSAF



9.7. PROMIS-PF 10b