Statistical Analysis Plan

Title: A Phase 2a evaluation of PLN-74809 on $\alpha_v\beta_6$ receptor occupancy using PET imaging in participants with IPF

Protocol Number: PLN-74809-IPF-201

Protocol Version: 6.0, Issue Date: 26 Oct 2021

SAP Version 2.0

SAP Issue Date: 16 Nov 2022

[redacted]

Previous SAP Versions

Not Applicable

SAP Amendments Before Database Lock

Version	Issue Date	Section	Revision / Addition	Rationale
2.0	16 Nov 2022	6.1 and 9	New analysis population (ITT Population).	To include participants that were enrolled, but early terminated prior to dosing in disposition outputs.
		6.1 and 9	Change "mITT Population" so that a post-baseline scan is also required.	To exclude participants that have a baseline PET scan, but no post-baseline PET scans.
		6.4 and 11	Update participant disposition tables and listings to be based on the ITT Population.	To include participants that were enrolled, but early terminated prior to dosing in these outputs.
		6.4 and 11	Update analysis population tables and listings to be based on the Screened Participants population.	To include all analysis populations.
		6.6	Remove GAP score from baseline characteristics summaries.	Not a relevant summary.
		6.9	Remove summary of partial/ complete dosing.	To be consistent with the most recent CRF.
		6.11.1 and 11	Change AE overall summary table to TEAE overall summary table.	Summary of AE that are not treatment-emergent is unnecessary. Listing these AEs will be sufficient.
		6.11.4	[redacted]	[redacted]
		11	Remove text "Adverse Events," from AE tables.	Simplify titles and remove association with non-treatment emergent AEs.

Version	Issue Date	Section	Revision / Addition	Rationale
2.0	16 Nov 2022	11	Update title of SOC listing.	To reflect the content of the listing more accurately.
		11	[redacted]	[redacted]
		11	Update analysis population for protocol deviations listing.	To include participants that were enrolled, but early terminated prior to dosing.

List of Abbreviations and Definitions of Terms

Abbreviation or Specialist Term	Explanation
AE	adverse event
ATC	anatomical therapeutic chemical
BLQ	below the lower limit of quantification
BMI	body mass index
CR	code review
CS	clinically significant
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
CV%	coefficient of variation
DLCO	diffusing capacity of the lungs for carbon monoxide
DSMB	data safety monitoring board
[redacted]	[redacted]
eCRF	electronic case report form
EOS	end of study
EOT	end of treatment
ET	early termination
FVC	forced vital capacity
GAP	gender, age and physiology
HRCT	high-resolution computerized tomography
IP	independent programming of values and manual review of format
IPF	idiopathic pulmonary fibrosis
ITT	intention to treat
max	maximum
MedDRA	Medical Dictionary of Regulatory Activities
min	minimum
mITT	modified intention to treat
MR	manual review
NCS	not clinically significant
PD	pharmacodynamics
PET	positron emission tomography
PI	principal investigator
PK	pharmacokinetics
SAE	serious adverse event
SAP	statistical analysis plan

Abbreviation or Specialist Term	Explanation
SD	standard deviation
Stat IP	independent programming by statistician of values and manual review of format
TEAE	treatment-emergent adverse event
TFL	tables, figures, and listings
WHODD	World Health Organization Drug Dictionary

Table of Contents

1 INTRODUCTION

This document details the planned statistical analyses for Pliant Therapeutics Inc's study PLN-74809-IPF-201, titled "A Phase 2a evaluation of PLN-74809 on $\alpha_v\beta_6$ receptor occupancy using PET imaging in participants with IPF".

Analyses of the positron emission tomography (PET) imaging data will be detailed in a separate analysis plan, written by [redacted].

The proposed analyses are based on the contents of the amended version of the protocol (version 6.0, dated 26 Oct 2021).

This is an open-label study in which up to 12 participants with idiopathic pulmonary fibrosis (IPF) will receive up to 2 doses of PLN-74809, starting at 60 mg [redacted] or 80 mg [redacted]). Higher planned doses, including 120, 240, and 320 mg, will also be evaluated, [redacted] All participants will undergo PET imaging at baseline and on the day of PLN-74809 dosing.

Eligible participants consenting to receive a maximum of 4 different single doses of PLN-74809 (eg, 60 and 120 mg) will need to undergo a ≥14-day washout between doses and will not need to repeat the baseline PET imaging.

1.1 Schedule of Events

Study Period	Screening[m,n]	Baseline[m,n]	Dosing Day						Day 2 (or Day 9)	EoT/EoS/ET
Study Day	Day -35 to Day -8	Day -7	Day 1 (or Day 8[a])							Day 8 (or Day 15) (±2 days)
Hours after Dose			0[b]	0.5	1	2	3	4		
Informed consent, medical history, demographics	●									
Check inclusion exclusion criteria	●	●								
Physical examination[c]	●	●	●							●
Vital signs (post 3 minutes, supine)	●	●	●							●
[redacted]										
Hematology and clinical chemistry[d]	●	●	●						●	●[o]
Urinalysis[e]	●	●	●							●
Urine pregnancy test (females only)		●								
FVC	●									
DLco	●									
Volumetric HRCT (quantitative)[f]	●									
PET imaging		●						●[g]		
Blood samples for radiotracer PK		●						●[h]		
[redacted]										
Study drug administration (PLN-74809)[i]			●							
Blood sample for PLN-74809 PK [d]			●	●	●	●	●	●	●[j]	
[redacted]										
Adverse events[l]	●	●	●	●	●	●	●	●	●	●
Concomitant medications[l]	●	●	●	●	●	●	●	●	●	●

[redacted]; EOT: end of treatment; EOS: end of study; ET: early termination; FVC: forced vital capacity; HRCT: high-resolution computerized tomography; PET: positron emission tomography; PK: pharmacokinetic.

[a] In case the PET ligand cannot be successfully synthesized on the scheduled day, participants will wait at least 1 week and then be dosed again for a second attempt at PET synthesis and imaging.

[b] Time 0 refers to immediately predose.

[c] Complete physical examination at screening and directed physical examination thereafter.

[d] A table of blood volumes is provided in Appendix 3 of the protocol (version 6.0, dated 26 Oct 2021).

[e] Urinalysis: dipstick followed up by microscopic examination if needed.

[f] An HRCT at screening may not be needed if a scan that meets the quality necessary for diagnosis purposes exists. If an HRCT is performed at screening, a second one is not needed during PET. An HRCT during PET may be performed if the screening HRCT is not adequate for the assessment of HRCT-PET relationship.

[g] PET to be performed at least 4 hours post-dose and no more than 30 minutes after the 4 hour PK time point.

[h] Blood samples for radiotracer PK to be taken 1, 3, 5, 10, 30, and 60 minutes after completion of radiotracer injection for PET-CT. Each collection time point has a +4-minute window. Refer to the Radiology Manual for details of sample collection including definitive information about allowable windows.

[i] Dosing to occur in connection to PET synthesis and availability.

[j] Day 2 plasma PK sample to be collected 24 hours post-dose.

[redacted]

[l] Adverse events and concomitant medications to be collected at each visit.

[m] For participants testing 2 different doses of PLN-74809, the Baseline PET scan will be based on the first single dose screening and not repeated. Additionally, if in the opinion of the Investigator, there is no clinical decline, the other screening and baseline procedures do not have to be repeated. Participants must undergo at least a 14-day washout period prior to testing the second dose level of PLN-74809.

[n] Screening and baseline visit may occur on the same day, duplicative assessments will not need to be repeated.

[o] Hematology and clinical chemistry may be conducted outside of study institution for EOS visit, if appropriate.

2 STUDY OBJECTIVES

2.1 Primary Objective

The primary objective is the evaluation of $\alpha_v\beta_6$ receptor occupancy by PLN-74809 in the lungs, as assessed by changes from baseline in $\alpha_v\beta_6$ PET tracer uptake patterns following a single dose.

Analyses of the PET imaging data will be detailed in a separate statistical analysis plan (SAP), written by [redacted].

2.2 Secondary Objectives

The secondary objective is the assessment of the safety and tolerability of PLN-74809 in IPF participants.

2.3 Exploratory Objectives

[redacted]

3 ENDPOINTS

3.1 Primary Endpoint

The primary endpoint is the changes from baseline in αvβ6 PET tracer uptake patterns following a single dose.

Analyses of the PET imaging data will be detailed in a separate analysis plan, written by [redacted]

3.2 Secondary Endpoints

1. Incidents of Treatment-Emergent Adverse Events (TEAE)
2. Change from baseline in clinical safety laboratory measures
3. Change from baseline in vital signs
4. [redacted]

3.3 Exploratory Endpoints

[redacted]

4 SAMPLE SIZE

The sample size has been set empirically. Up to 12 participants should provide proof of concept on the ability of the study to assess target engagement ($\alpha_v\beta_6$ receptor occupancy by PLN-74809). Pharmacodynamic (PD), pharmacokinetic (PK), and safety/ tolerability evaluation of PLN-74809 will be assessed in the target population.

5 RANDOMIZATION

Not applicable. This a non-randomized, open-label study.

6 PLANNED ANALYSES

6.1 Analysis Populations

Participants excluded from the analysis populations and the reason for their exclusion will be listed in Appendix 16.2 of the clinical study report (CSR).

6.1.1 Screened Participants

Screened Participants are any participants who gave informed consent to participate in the study.

6.1.2 Intention to Treat (ITT) Population

All participants enrolled in the study (passed screening) will be included in the ITT Population.

6.1.3 Safety Population

All participants who receive at least 1 dose of study drug will be included in the Safety Population.

6.1.4 Modified Intention to Treat (mITT) Population

All dosed participants with at least baseline and at least 1 post-baseline PET scan will be included in the mITT population.

The mITT Population will not be used for any analyses listed in this SAP, with the exception of participant disposition.

6.1.5 PK Concentration Population

All participants who receive at least 1 dose of study drug and have any measurable PLN-74809 concentration data will be included in PK Concentration Population.

6.1.6 PK Analysis Population

All participants who have sufficient PLN-74809 concentration data for PK calculation will be included in the PK Analysis Population.

6.2 Derived Data

This section describes the derivations required for statistical analysis. Unless otherwise stated, variables derived in the source data will not be re-calculated.

6.2.1 Race

Where more than 1 race category has been selected for a participant, these race categories will be combined into a single category labeled "Multiple Race" in the summary tables. The listings will reflect the original selected categories.

6.2.2 Body Mass Index

Body mass index (BMI) will be calculated as follows:

BMI (kg/m^2) = Weight at screening (kg) / [Height at screening $(m)^2$]

6.2.3 Baseline

Baseline is defined as the last non-missing value (either scheduled, unscheduled or repeat) before the participant receives the first dose of study drug.

6.2.4 Dose-specific Baseline

Dose-specific baseline is defined as the last non-missing value (either scheduled, unscheduled or repeat) before the participant receives the specific dose of study drug being analyzed.

6.2.5 End of Dosing Period

For doses that are not a participant's final dose of the study, end of dosing period is defined as the last non-missing visit prior the next dose.

For participants' final dose of the study, end of dosing period is defined as the end of treatment (EOT)/ end of study (EOS) visit.

6.2.6 Gender, Age and Physiology (GAP) Index and Staging System

The GAP index and staging system is a multidimensional prognostic staging system derived from 4 commonly measured clinical and physiologic variables (Gender, Age and 2 lung physiology variables (forced vital capacity [FVC] and diffusing capacity of the lungs for carbon monoxide [DLCO])[3]. Points are allocated to each clinical or physiological variable and points are summed to provide a total score (from 0-8). The total score is then used to assign a stage (I, II, or III) as follows:

GAP Scoring

Predictor	Points Allocated
Gender	Female = 0 Male = 1
Age	≤ 60 = 0 61 - 65 = 1 > 65 = 2
Physiology – FVC, % Predicted	> 75 = 0 50 - 75 = 1 < 50 = 2
Physiology – DLCO, % Predicted	> 55 = 0 36 - 55 = 1 ≤ 35 = 2 Cannot perform[a] = 3
Total Point Score	**0 - 8**

[a] 'Cannot perform' is only assigned if symptoms or lung function prohibited performance of the DLCO maneuver. If DLCO is unavailable for a non-respiratory reason (eg, an operational reason), the GAP index and staging system cannot be applied.

Staging System

Stage	I	II	III
Points	0 - 3	4 – 5	6 - 8

6.2.7 Duration of Nintedanib and Pirfenidone

Duration of nintedanib will be calculated in months as: date of first dose of study drug – date of first dose of nintedanib.

Duration of pirfenidone will be calculated in months as: date of first dose of study drug – date of first dose of pirfenidone.

6.2.8 Early Termination Assessments

Early Termination (ET) assessments of physical examinations, vital signs, [redacted] hematology, clinical chemistry, urinalysis will be summarized with the nearest scheduled visit. If the visit already has data, then the result will be binned toward the next scheduled visit.

Methods for analyzing ET assessments of PET imaging data will be detailed in a separate analysis plan, written by [redacted]

6.2.9 Duration / Study Period / Study Day / Time

Study day within each dosing period will be calculated as the number of days from the dose of study drug within the given dosing period.

For events on or after the dose of study drug within the given dosing period:

- Study day = date of event – date of first dose of study drug + 1.

For events before the dose of study drug within the given dosing period:

- Study day = date of event – date of first dose of study drug.

Study day should always be presented in listings along with the dosing period it is relative to (ie "Period X Day X").

6.2.10 Conventions for Missing and Partial Dates

All rules explained below for partial / missing dates will be followed unless contradicted by any other data recorded on the electronic Case Report Form (eCRF).

All dates presented in the individual participant listings will be as recorded on the eCRF (ie, not completed as per the below rules).

6.2.10.1 Missing / Partial Start / Stop Date of Adverse Events, Medical History and Concomitant Medications

Missing and partial start dates will be imputed solely for the purpose of determining whether an AE is treatment-emergent, medical history is ongoing at screening, or a medication is concomitant to study drug.

Partial or missing stop date will be imputed as follows:

If the stop date is completely missing and the event has resolved, or the participant has stopped taking the concomitant medication, the stop date will be imputed as the date of the participant's last clinic visit in the study.

- If only the year is known, the stop date will be imputed as "31-Dec" of that year or as the date of the participant's last clinic visit in the study if in the same year.
- If the month and year are known, the stop date will be imputed as the last day of that month unless the stop date corresponds to the same month as the participant's last clinic

visit in which case the date of participant's last clinic visit in the study will be used instead.

Missing start date will be imputed as follows:

- If the stop date occurs on or after the start of study drug or the event / concomitant medication is ongoing, the start date will be imputed as the date of the first dose of study drug.
- If the stop date occurs before the start of study drug, the start date of the event / concomitant medication will be imputed as the participant's screening date or the stop date of the event / concomitant medication whichever the earlier.

Partial start date (year present, but month and day missing)

- If the stop date occurs on or after the start of study drug or the event / concomitant medication is ongoing, and the year is the same as the year of first dosing the start date will be imputed as "01-Jan" of the same year or the date of the first dose of study drug whichever is latest. If the year is different from the year of first dosing "01-Jan" will be used.
- If the stop date occurs before the start of study drug, the start date of the event / concomitant medication will be imputed as the "01-Jan" of the same year.

Partial start date (month and year present, but day missing)

- If the stop date occurs on or after the start of study drug or the event / concomitant medication is ongoing, the start date will be imputed as the first day of the same month and year unless this partial start date is in same month as the first dose of study drug in which case the date of first dose of study drug will be used.
- If the stop date occurs before the start of study drug, the start date will be imputed as the first day of the month and year of the partial stop date.

If the start time is missing it will be imputed only in the case where the start date of the concomitant medication / event corresponds to the date of the first dose of study drug. The time will be imputed as the same time as the first dose of study drug. In all other cases the time will not be imputed.

6.2.11 Unscheduled Visits

For table summaries of observed and change from baseline values, only scheduled post-baseline values will be tabulated. Post-baseline repeat / unscheduled assessments will be disregarded.

For shift tables, scheduled post-baseline, repeat post-baseline, and unscheduled post-baseline values will be tabulated, group by study day.

All post-baseline assessments will be listed in the relevant appendices to the CSR.

6.3 Conventions

All clinical data listings, summaries, figures and statistical analyses will be generated using SAS® [redacted]. Summaries of the clinical data will be presented by dose or overall.

Continuous variables will be summarized by the number of non-missing observations (n), mean, standard deviation (SD), median, minimum (min) and maximum (max).

Categorical variables will be summarized by presenting the frequency and percent. Percentages will be based on the number of non-missing observations or the participant population, unless otherwise specified. For each variable, all categories will be shown. Zero frequencies (but not the percent) within a category will be presented.

PK data listings, summaries, figures, and statistical analyses will be generated using Phoenix® WinNonlin® [redacted] or SAS® [redacted].

PK data (concentration-time data and PK parameters) will be summarized by the number of non-missing observations (n), arithmetic mean (mean), SD, median, min, max, coefficient of variation (CV%), geometric mean, and geometric CV%.

6.3.1 Dose Labels

Dose labels will be displayed in the tables, figures and listings (TFLs) as follows:

60 mg	80 mg	120 mg	240 mg	320 mg	Overall

6.3.2 Decimal Places

Listings, minimum and maximum will contain the number of decimal places that is clinically meaningful specific to each parameter. Means, medians and percentiles will be displayed to 1 more decimal place than min and max. Dispersion statistics (eg standard deviation) will have 2 more decimal places than min and max. Percentages will be displayed with 1 decimal place.

For PK data, individual concentrations and PK parameters will be reported to 3 significant figures. For summary statistics, n will be reported as a whole number; mean, SD, median, min, max, geometric mean, CV%, and geometric mean CV% will be reported to the same precision as for individual data.

6.4 Participant Disposition

Participant disposition will be summarized as follows:

- The number of participants who are in each analysis population will be summarized overall for Screened Participants.
- The number of early withdrawals and the reasons for withdrawals will be tabulated by dose and overall for the ITT Population.
- The number of screened participants, rescreened participants, and screen failures and the reasons for screen failure will be tabulated overall for the Screened Participants population.

6.5 Protocol Deviations

A listing of protocol deviations will be provided within Appendix 16.2 of the CSR.

6.6 Baseline Comparability

The comparability of doses with respect to participant demographics and baseline characteristics will be assessed in a descriptive manner, but no formal statistical testing will be performed.

Standard continuous or categorical variable summaries will be presented overall for the following variables based on the Safety Population:

- Age at Informed Consent (years),
- Sex (Male, Female),
- Fertility Status (Childbearing Potential, Post-menopausal, Surgically Sterile)
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino),

- Race (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White, Multiple Race),
- Height at Screening (cm),
- Weight at Screening (kg),
- BMI at Screening (kg/m^2)
- Pulmonary Function at Screening,
- DLCO,
- GAP Staging,
- Months since IPF diagnosis,
- Received nintedanib as standard of care prior to randomization (Yes, No),
    - If yes, duration of nintedanib use (months),
- Received pirfenidone as standard of care prior to randomization (Yes, No),
    - If yes, duration of pirfenidone use (months)

All demographic and baseline characteristic data will be listed.

6.7 Medical History

The number of participants with previous and ongoing conditions at screening will be summarized by system organ class and preferred term for the Safety Population. Previous and ongoing conditions at screening will be listed for the Safety Population. Conditions will be presented by Medical Dictionary of Regulated Activities (MedDRA) (version 4.0) system organ class and preferred term.

6.8 Prior and Concomitant Medications and Non-Pharmacological Procedures

The number of prior and concomitant medications will be summarized by Anatomical Therapeutic Chemical (ATC) Classification level 4 term and preferred term for the Safety Population. Prior and concomitant medications will be summarized separately. Prior and concomitant medications and non-pharmacological procedures will be listed for the Safety Population. Medications will be coded using the World Health Organization Drug Dictionary (WHODD) [redacted] ATC Classification System level 4 term and preferred term.

Prior medications are defined as all medications starting and stopping before the date of first dose of study drug. Concomitant medications are defined as medications taken on or after the date of first dose of study drug.

Use and duration of Pirfenidone and Nintedanib will be summarized overall using standard continuous or categorical variable summaries.

6.9 Exposure to Study Drug

The number of participants who have received each dose, and the order received, will be summarized by dose and overall, for the Safety Population.

All dosing information will be listed.

6.10 Statistical Analysis of Pharmacokinetic Data

6.10.1.1 Concentration-time Data

Plasma samples for PK analysis will be obtained predose and at 0.5, 1, 2, 3, and 4 hours after dosing on Day 1 (prior to receiving the R01 Knottin tracer) and at 24 hours after dosing (Day 2). A collection window of ±5 minutes will be allowed for samples up to 1-hour post-dose and a collection window of ±10 minutes will be allowed for samples that are collected at 2 hours post-dose and after. Concentrations collected significantly outside of the collection windows will be discussed with the Sponsor prior to summarizing concentration-time data.

The percent (%) unbound PLN-74809 will also be determined at 0.5, 1, 2, 3, and 4, and 24 hours after dosing on Day 1. Unbound plasma PLN-74809 concentrations will be calculated as percent unbound x total plasma concentration at each time point.

Plasma PLN-74809 concentrations (total and unbound) at each sampling time point will be presented in listings and summarized by dose with descriptive statistics. Mean plasma (total and unbound) PLN-74809 concentration-versus-time profiles (with plasma concentrations on both a log and linear scale) will be plotted for each dose. Concentration-versus-time plots will also be provided for each participant. For presentation of the individual data and summary statistics, concentrations below the limit of quantitation (BLQ) will be set to zero. Percent unbound at each time point will be presented in listings and summarized by dose with descriptive statistics. BLQ values will be presented as BLQ (<1.00 ng/mL) in the concentration listing (ie, these will not be set to zero).

6.10.1.2 PK Parameters

Concentration-time data for PLN-74809 will be analyzed using noncompartmental methods in Phoenix® WinNonlin® [redacted] in conjunction with the internet-

accessible implementation of Pharsight® Knowledgebase Server™ [redacted]

During the PK analysis, BLQ concentrations up to the time of the first quantifiable concentration will be treated as zero. Embedded (values between 2 quantifiable concentrations) and terminal BLQ concentrations will be treated as "missing". PK analysis will be performed using actual time relative to dosing. Descriptive statistics will be used to summarize the PK parameters by dose. Individual PK parameters will be provided in listings. Subjects will be referred to as "participant".

The following PK parameters will be calculated for PLN-74809 in plasma:

Parameter	Definition
C_{max}	Maximum observed plasma drug concentration, determined directly from individual concentration-time data
T_{max}	Time to maximum observed plasma concentration, determined directly from individual concentration-time data
AUC_{0-4}	Area under the plasma concentration-time curves from time 0 to 4 hours postdose Calculated using Linear-Up Log-Down Method
AUC_{0-24}[a]	Area under the plasma concentration-time curves from time 0 to 24 hours postdose Calculated using Linear-Up Log-Down Method
AUC_{last}	Area under the plasma concentration-time curves from time 0 to the time of the last detectable concentration Calculated using Linear-Up Log-Down Method
C_{avg}[a]	Average concentration Calculated as $AUC_{0-24}/24$
$C_{max, u}$	Unbound C_{max}, calculated using unbound plasma concentrations.
$AUC_{0-4, u}$	Unbound AUC_{0-4}, calculated using unbound plasma concentrations
$AUC_{0-24, u}$[a]	Unbound AUC_{0-24}, calculated using unbound plasma concentrations
$AUC_{last, u}$	Unbound AUC_{0-24}, calculated using unbound plasma concentrations
$C_{avg, u}$	Unbound C_{avg}, calculated as $AUC_{0-24,u}/24$

[a] As no samples were collected between 4 and 24 hours, total and unbound AUC_{0-24}, AUC_{last}, C_{avg} may be overestimated. AUC_{0-24} may be overestimated by approximately 12%. This may be discussed in the CSR as warranted.

The validated method used for this study:

[redacted]

6.11 Safety Analyses

The safety analyses will be presented by the dose received for the Safety Population.

6.11.1 Adverse Events

A TEAE is defined as:

- Any AE that has an onset on or after the first dose of study drug.
- Any pre-existing AE that has worsened in severity on or after the first dose of study drug.

AEs will be classified as either related or not related to the study drug. If an AE has missing relationship, it is assumed to be related to the study drug for analysis purposes.

AEs will also be classified as either related or not related to study procedure. If an AE has missing relationship, it is assumed to be related to study procedure for analysis purposes.

Severity of the AE will be graded using the Common Terminology Criteria for Adverse Events (CTCAE) grading system (Version 5.0): Grade 1 (Mild), Grade 2 (Moderate), Grade 3 (Severe), Grade 4 (Life-Threatening), Grade 5 (Death). Grade 3 (Severe) will be assumed for an AE with missing grade.

The following tables will be presented for AEs:

- Number (%) of participants with TEAEs, study drug-related TEAEs, procedure-related TEAEs, serious TEAEs, TEAEs leading to withdrawal, and TEAEs leading to death, by dose and overall.
- Number (%) of participants with TEAEs by system organ class and preferred term, dose and overall.
- Number of events of TEAEs by system organ class and preferred term, dose and overall.
- Number (%) of participants with study drug-related TEAEs by system organ class and preferred term, dose and overall.
- Number (%) of participants with procedure-related TEAEs by system organ class and preferred term, dose and overall.
- Number (%) of participants with TEAEs by system organ class, preferred term, maximum severity, dose and overall.

- [redacted]
- Listing of Serious Adverse Events (SAEs) (presented in the Table section of the appendices).
- Listing of AEs leading to withdrawal from study (presented in the Table section of the appendices).
- Listing of AEs leading to death (presented in the Table section of the appendices).

[redacted]

In counting the number of AEs reported, a continuous event (ie reported more than once and which did not cease), will be counted only once; non-continuous AE reported several times by the same participant will be counted as multiple events.

Where a preferred term is reported more than once, the most related or maximum severity will be counted.

When summarizing TEAEs by dose, TEAEs will be allocated to the most recent dose received prior to onset of the TEAE. TEAEs that increase in severity will be counted as a separate TEAE and allocated to the most recent dose received prior to the increase in severity.

All AEs will be listed.

6.11.2 Laboratory Data

Descriptive statistics of the observed values and change from baseline in each hematology, urinalysis (continuous parameters only) and clinical chemistry parameter will be presented by

dose at each time point after the first dose of study drug. Descriptive statistics of the observed values in each urinalysis (categorical parameters only) parameter will be presented by dose at each time point after the first dose of study drug.

Clinical laboratory test parameters will be listed, using the CTCAE grading scale, for individual participants, with values outside the reference ranges flagged. The incidence of treatment-emergent laboratory abnormalities will be summarized by severity. Summary statistics will be calculated for each parameter.

Data will be presented using the original unit of measurement as reported by the laboratory used.

Each measurement will be classified as below, within, or above normal range, based on ranges supplied by the laboratory used. Additionally, abnormal measurements will also be categorized as clinically important/ significant or not, based on principal investigator (PI) judgement. Shift tables in relation to the normal range from baseline will be presented by dose at each time point after the first dose of study drug.

All laboratory data will be listed. (Pregnancy test data will be listed only.) Abnormal laboratory data will also be listed separately.

6.11.3 Vital Signs

Descriptive statistics for observed values and changes from baseline in the following vital signs will be presented by dose at each time point after dosing of study drug:

- Systolic blood pressure (mmHg)
- Diastolic blood pressure (mmHg)
- Pulse rate (bpm)
- Ear temperature (ºC)
- Pulse oximetry (SpO_2)

6.11.4 [redacted]

[redacted]

[redacted]

6.11.5 Physical Examination

Shift tables for the observed status of each of the body systems (Normal, Abnormal NCS, and Abnormal CS) from baseline to each time point after dosing of study drug will be presented.

All data, including details of clinically significant findings will be listed.

6.11.6 Pregnancy Report

If there are any pregnancies reported, then all related data will be listed.

7 INTERIM ANALYSIS

No interim safety analyses are planned. Preliminary PK results are reviewed on an ongoing basis.

8 DATA SAFETY MONITORING BOARD ANALYSIS

Not applicable. The study did not have a Data Safety Monitoring Board (DSMB).

9 CHANGES TO PLANNED PROTOCOL ANALYSIS

The analysis plans detailed throughout this document have changed from the planned analyses described in the protocol v6.0 (dated 26 Oct 2021) in the following ways.

9.1 Analysis Populations

The PET Population has been renamed the mITT Population. The definition has also been updated to require at least 1 post-baseline PET scan.

[redacted]

An additional analysis population has been defined: ITT Population. This population will be used for all disposition TFLs to include participants that were enrolled, but early terminated prior to dosing.

10 REFERENCES

[redacted]

11 LIST OF TABLES, FIGURES AND LISTINGS

The following table includes details of the tables, figures and listings to be included within each section of the eCTD. The eCTD section is shown in bold. The following validation methods maybe used:

- Independent programming of values and manual review of format (IP)
- Independent programming by statistician of values and manual review of format (Stat IP)
- Manual review (MR)
- Code review (CR)

Section Number	Table Number	Table Title	Validation Method	Shell Number (if repeat)
14.1	[redacted]			
14.1.1				
14.1.2				
14.1.2				
14.2				
14.3				
14.3.1				

Section Number	Table Number	Table Title	Validation Method	Shell Number (if repeat)
[redacted]				
14.3.2				
14.3.3				
14.3.4				
14.3.5				
14.3.6				
14.3.7				

Section Number	Table Number	Table Title	Validation Method	Shell Number (if repeat)
	[redacted]			
14.3.8				
14.4				

Section Number	Table Number	Table Title	Validation Method	Shell Number (if repeat)
	[redacted]			
14.5				
14.6				

Section Number	Figure Number	Figure Title	Validation Method	Shell Number (if repeat)
14.4	[redacted]			

Section Number	Listing Number	Listing Title	Validation Method	Shell Number (if repeat)
16.2	[redacted]			
16.2.1				
16.2.2				
16.2.3				
16.2.4				
16.2.5				
16.2.6				
16.2.7				

Section Number	Listing Number	Listing Title	Validation Method	Shell Number (if repeat)
16.2.8	[redacted]			