Statistical Analysis Plan

A randomized, double-blind, dose-ranging, placebo-controlled, Phase 2a evaluation of the safety, tolerability, and pharmacokinetics of PLN-74809 in participants with primary sclerosing cholangitis (PSC) and suspected liver fibrosis (INTEGRIS-PSC)

Protocol Number: *PLN-74809-PSC-203*

Protocol Version: *Parallel Version 1.1(Amendment 4),* [redacted]

Sequential Version 1.0 (Amendment 4), [redacted]

SAP Version 2.0, issued 04 AUG 2023

[redacted]

Previous SAP Versions

SAP Version *1.0,* [redacted]

[redacted]

[redacted]

Table of Contents

LIST OF ABBREVIATIONS

Abbreviation	Definition
ADL	activities of daily living
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
ARDS	acute respiratory distress syndrome
AST	aspartate aminotransferase
AUC	area under the plasma concentration-time curve
AUC_{0-24}	area under the plasma concentration-time curve from time zero to 24 hours
BALF	bronchoalveolar lavage fluid
[redacted]	[redacted]
C_{max}	maximum plasma drug concentration
CA199	carbohydrate antigen 199
CCA	cholangiocarcinoma
CFR	Code of Federal Regulations
COVID-19	coronavirus disease 2019
CRO	contract research organization
CTCAE	Common Terminology Criteria for Adverse Events
[redacted]	[redacted]
[redacted]	[redacted]
DSMB	Data Safety Monitoring Board
[redacted]	[redacted]
eCRF	electronic case report form

ELF	Enhanced Liver Fibrosis (score)
EoS	end of study
EoT	end of treatment
ERCP	endoscopic retrograde cholangiopancreatography
ET	early termination
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
GGT	gamma-glutamyl transferase
HIPAA	Health Information Portability and Accountability Act
HIV	human immunodeficiency virus
IBD	inflammatory bowel disease
IC_{50}	50% inhibitory concentration
IC_{80}	80% inhibitory concentration
IC_{90}	90% inhibitory concentration
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	independent ethics committee
[redacted]	[redacted]
INR	international normalized ratio
IRB	institutional review board
IRT	interactive response technology
kPa	kilopascal
[redacted]	[redacted]
LDH	lactic dehydrogenase
[redacted]	[redacted]
LSM	liver stiffness measurement

MAD	multiple ascending dose
[redacted]	[redacted]
MedDRA	Medical Dictionary for Regulatory Activities
MELD	model for end stage liver disease
MR	magnetic resonance
MRCP	magnetic resonance cholangiopancreatography
NCI	National Cancer Institute
NOAEL	no observed adverse effect level
[redacted]	[redacted]
OHP	hydroxyproline
PD	pharmacodynamic(s)
[redacted]	[redacted]
PIPEDA	Personnel Information Protection and Electronic Documents Act
PK	pharmacokinetic, pharmacokinetics
PROs	participant-reported outcomes
PSC	primary sclerosing cholangitis
pSMAD2/3	phosphorylated SMAD2/3
PTC	percutaneous transhepatic cholangiography
REB	research ethics board
SAD	single ascending dose
SAE	serious adverse event
[redacted]	[redacted]
SMAD2/3	family of proteins similar to the gene products of the Drosophila gene 'mothers against decapentaplegic' (*Mad*) and the *C. elegans* gene Sma, 2 or 3
TE	transient elastography
TEAE	treatment-emergent adverse event
TGFβ	transforming growth factorbeta
TNFα	tumor necrosis factor-alpha

UDCA	ursodeoxycholic acid
ULN	upper limit of normal

1 INTRODUCTION

This document details the planned statistical analyses for Pliant Therapeutics Inc. Study PLN-74809-PSC-203, "A randomized, double-blind, dose-ranging, placebo-controlled, Phase 2a evaluation of the safety, tolerability, and pharmacokinetics of PLN-74809 in participants with primary sclerosing cholangitis (PSC) and suspected liver fibrosis (INTEGRIS-PSC)".

The proposed analyses are based on the contents of the [redacted]

This is a Phase 2a, multicenter, 3-part, randomized, double-blind, dose-ranging, placebo-controlled study to evaluate the safety, tolerability, and PK of once-daily (QD) treatment with PLN-74809 in male and female participants aged 18 to 75 years with an established diagnosis of large duct PSC and suspected liver fibrosis. Part 1 will evaluate 40 mg PLN-74809 and placebo, Part 2 will evaluate 80 and 160 mg PLN-74809 and placebo and Part 3 will evaluate 320 mg PLN-74809 and placebo. Placebo participants will be pooled across the study when comparing to PLN-74809 treatment groups.

Each study part will include an up to 42-day screening period, followed by a treatment period of either 12 weeks (Parts 1 and 2) or at least 24 weeks and up to 48 weeks (Part 3), and finally a 4-week post-treatment follow-up period. Based on regulatory considerations, randomization to dose level in Part 2 of the protocol (80 or 160 mg PLN-74809) was conducted in either parallel or sequential manner.

Each participant in Parts 1 and 2 will participate in the study for approximately 154 days (22 weeks), including screening, treatment, and post-treatment safety follow-up. The duration for Part 3 of the study will be variable depending on the study enrollment rate. The duration of participation will be approximately 238 days (34 weeks) for the last participant enrolled and approximately 406 days (58 weeks) for the first participant enrolled including screening, treatment, and post-treatment safety follow-up. The end of Part 3 will commence once the last participant reaches 24 weeks of treatment. At that time, all study participants will complete their next scheduled visit (End of Treatment [EOT]) and the 4 weeks of follow up (End of Study [EOS]). The end of study is defined as the last visit of the last participating participant.

2 STUDY OBJECTIVES

2.1 Primary Objective

The primary objective of this study is to assess the safety and tolerability of PLN-74809 in participants with PSC and suspected liver fibrosis.

2.2 Secondary Objective

The secondary objective of this study is to assess the PK of PLN-74809 in participants with PSC and suspected liver fibrosis.

2.3 Exploratory Objectives

The exploratory objectives of this study are as follows:

- To assess changes from baseline in liver fibrosis biomarkers, [redacted] PRO-C3 and Enhanced Liver Fibrosis (ELF) score
- To assess changes from baseline in alkaline phosphatase (ALP)
- To assess changes from baseline in magnetic resonance (MR)-based liver imaging
- To assess changes from baseline in patient-reported outcomes (PROs)

3 ENDPOINTS

3.1 Primary Safety Endpoint

The primary safety endpoint is the incidence of treatment-emergent adverse events (TEAEs).

3.2 Secondary Safety Endpoints

The secondary safety endpoints are:

- Clinical laboratories, including hematology, serum chemistry, coagulation, and urinalysis
- [redacted]
- Vital signs measurements

3.3 Secondary Pharmacokinetic Endpoints

The secondary PK endpoints are plasma PLN-74809 concentrations [redacted] at each sampling time point.

3.4 Exploratory Endpoints

The following exploratory endpoints will be reported:

- Liver fibrosis markers (PRO-C3, [redacted]
- Liver function markers (ALP, [redacted]
- Magnetic resonance (MR)-based liver imaging parameters (Whole liver [redacted] gadoxetate MRI relative enhancement (RE), Bile duct [redacted] gadoxetate MRI time of arrival)
- PROs [redacted] Partial Mayo Score (PMS) parameters)

3.5 Additional Endpoints

The following additional endpoints will be reported:

- FibroScan liver stiffness (kPa)

4 SAMPLE SIZE

The sample size was determined empirically. A sample size of approximately 21 participants per treatment group exposed to PLN-74809 is expected to provide a meaningful evaluation of the safety, tolerability, and PK of PLN-74809 in the target population.

5 RANDOMIZATION

For each planned PLN-74809 dose in each Part of the study, n=21 subjects will be randomized to PLN-74809 and n=7 participants will be randomized to placebo for a total of n=28 and in total, N=112 for 4 PLN-74809 doses (40, 80, 160 and 320 mg).

Approximately 112 participants may be enrolled in this study (28 participants in Part 1, 56 participants in Part 2, and 28 participants in Part 3).

Part 1: 28 eligible participants will be randomized in a 3:1 ratio (40 mg PLN-74809:placebo).

Part 2: 28 eligible participants per cohort (56 in total) will be randomized in a 3:1 ratio (PLN-74809:placebo). PLN-74809 doses administered in each cohort will be 80 mg or 160 mg.

Part 3: 28 eligible participants will be randomized in a 3:1 ratio (320 mg PLN-74809:placebo).

Randomization will be stratified by use of ursodeoxycholic acid (UDCA) (yes/no).

Participants will be centrally randomized at the baseline visit using an interactive response technology (IRT) system, according to a computer-generated randomization scheme. Randomization will occur immediately prior to the first dose (Day 1).

6 PLANNED ANALYSES

The Statistical Analysis Plan (SAP) will be approved prior to unblinding of the data for the Part 1/2 interim analysis. Additional statistical analyses or changes to the statistical analysis after this milestone will be documented in an addendum to the SAP.

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 CSR.

6.1.1 Screened Participants

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

6.1.2 Randomized Participants

Randomized participants are those who were assigned a randomization number.

6.1.3 Safety Population

The safety population is defined as all randomized participants who receive at least 1 dose of study drug. Treatment assignment will be summarized by actual treatment.

6.1.4 Pharmacokinetic Concentration Population

The PK concentration population is defined as all participants in the safety population who have any valid PLN-74809 concentration data not including BLQ values. Treatment assignment will be summarized by actual treatment.

6.1.5 Pharmacodynamic Analysis Population

The PD analysis population is defined as all participants in the safety population who have evaluable baseline and at least 1 evaluable postbaseline PD measurement. Treatment assignment will be summarized by actual treatment.

6.1.6 Efficacy Per Protocol Population

The Efficacy Per-Protocol population will consist of participants from the randomized population without protocol deviations that may significantly impact the interpretation of safety and/or efficacy analyses. Treatment assignment will be summarized by randomized treatment.

[redacted]

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 recalculated.

6.2.1 Race

When more than 1 race category has been selected for a participant, the race categories will be combined into a single category, labelled "Multiple Race," in the summary tables. The listings will reflect the originally 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 and Change from Baseline

Baseline is defined as the last non-missing value before the participant receives the first dose of study drug. Change from baseline is defined as the difference between baseline and any post-baseline records.

6.2.4 Study Day

Study day will be calculated as the number of days in relation to the first dose of study drug.

- date of event – date of first dose of study drug + 1, for events on or after first dose
- date of event – date of first dose of study drug, for events before first dose

6.2.5 Conventions for Missing and Partial Dates

Dates (historical or during study conduct) will only be imputed if a full date is needed for a calculation or to support a definition.

All dates presented in the individual participant listings will be as recorded on the electronic case report form (eCRF).

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

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 treatment.

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 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.

Missing Date of Last Dose

If date of last dose is not present, the date of completion/termination will be imputed as the date of last dose for calculation of study drug exposure.

6.2.6 Exposure to Study Drug

Duration of exposure to study drug will be calculated as follows:

- Date of last dose (or the date of completion/termination if not present) minus the date of first dose + 1.

The exposure calculation will not take into account breaks in therapy.

6.2.7 Study Drug Compliance

Study drug compliance will be calculated by comparing the amount of drug dispensed and drug returned for each participant as follows:

- Number [redacted] taken = Total dispensed – Total returned (if the number returned is missing, a value of 0 will be used).
- Expected number [redacted] = Number of days on study (calculated as per Section 6.2.6 for duration of exposure) × Number [redacted] for the relevant study part and dose group (per the table below).

Compliance (%) = (Number [redacted] taken / Expected number [redacted]) *100

[redacted]

6.2.8 Inexact Values

In the case where a variable is recorded as "> x", "≥ x", "< x" or "≤ x", a value of x will be taken for analysis purposes. All data will be presented as is for listing purposes.

6.2.9 Imperial to Metric Unit Conversion

Temperature collected in degrees Fahrenheit (°F) will be converted degrees Celsius (°C) using the following conversion calculations:

- $x\ (°C) = [x\ (°F) - 32] / 1.8$

[redacted]

[redacted]

[redacted]

[redacted]

6.3 Partial Mayo Score for Inflammatory Bowel Disease (IBD)

The partial Mayo score, range 0-9, with higher scores implying more severe disease will be derived as follows:

Partial Mayo Score = Stool frequency score (0-3) + Rectal bleeding score (0-3) + Physicians' global assessment (0-3).

[redacted]

[redacted]

[redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

- [redacted]
- [redacted]

[redacted]

[redacted]

- [redacted]
- [redacted]);

[redacted]

6.6 Early Termination Assessments

Unscheduled early termination assessments will not be summarized unless the early termination visit falls on a scheduled visit.

6.7 Unscheduled Visits

Only scheduled post baseline values will be tabulated. Post baseline repeat / unscheduled assessments will not be summarized but will be listed in the relevant appendices to the CSR.

6.8 Conventions

6.8.1 Medical Coding

Adverse events and medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) [redacted]. Conditions will be assigned to a system organ class and preferred term based on the Investigator-reported verbatim term.

Any medications taken (other than study drug) will be coded using the World Health Organization Drug Dictionary (WHO Drug) [redacted] Version. Medications (both prior and concomitant) will be assigned to an Anatomical Therapeutic Chemical (ATC) Level 4 drug classification and preferred name based on the medication name reported on the eCRF.

6.8.2 Data Handling

All clinical data programming will be performed using SAS® statistical software package [redacted] and based on Clinical Data Interchange Standards Consortium (CDISC) data standards.

[redacted]

6.8.3 Summary Statistics

Continuous variables will be summarized using an 8-point summary, the number of non-missing observations, mean, standard deviation, median, interquartile range (Q1, Q3), minimum (min), and maximum (max).

PK concentration data will be summarized using a 11-point summary, the number of non-missing observations (n), arithmetic mean (mean), standard deviation (SD), geometric mean, median, interquartile range (Q1, Q3), minimum (min), maximum (max), coefficient of variation (CV%) and geometric CV%

Categorical variables will be summarized by presenting the frequency and percent. Percentages will be based on the number of non-missing observations or the count in 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.

Incidences of AEs, medical history, and concomitant medications will be reported at the participant level. Participants can only be counted once within each preferred term and system organ class under the highest severity and relationship to study drug. Percentages will be calculated using the number of participants in the treatment group for the Safety Population.

6.8.4 Decimal Places

For summary statistics, n will be reported as a whole number. Means, medians, and percentiles will be displayed to 1 more decimal place than the data, dispersion statistics (eg, standard deviation) will have 2 more decimal places, and the minimum and maximum will be displayed to the same number of decimal places as reported in the raw data.

Where appropriate, less decimal places may be used on a case-by-case basis as denoted in the table shells.

Percentages will be displayed with 1 decimal place. All data presented in the individual participant listings will be as recorded on the eCRF.

6.8.5 Data Displays

All TFLs will be generated as individual Rich Text Format (.rtf) files using SAS [redacted]. Data summaries and graphical analyses will be reported within Section 14 of the CSR and individual participant data listings within Appendix 16.2 of the CSR.

Participant disposition, baseline characteristics, and demographics, will be presented by treatment group (including all PLN-74809) and overall. Other summaries will be presented by treatment group (including all PLN-74809) only.

Treatment group labels will be displayed as follows:

PLN-74809 40 mg (N=XX)	PLN-74809 80 mg (N=XX)	PLN-74809 160 mg (N=XX)	PLN-74809 320 mg (N=XX)	All PLN-74809 (N=XX)	Placebo (N=XX)

Listings will be sorted in the following order, study part (Parts 1, 2, and 3), treatment group, participant number, parameter, and visit unless otherwise stated. All data for randomized participants will be listed.

6.9 Participant Disposition

The overall total of participants in the screened population will be summarized. The number of participants randomized will be summarized by treatment group and overall.

Participant disposition will be summarized by treatment group and overall for the safety population, as follows:

- The number of participants in each analysis population (Safety, PK, and PD).
- The number of participants who complete the study drug.
- The number of participants who discontinue the study drug and the reason for discontinuation of study drug.
- The number of participants who complete the study.
- The number of participants who withdraw from the study and the reason for withdrawal.

6.10 Protocol Deviations

Number of participants with protocol deviations will be presented by treatment group, category, and classification (critical, major, minor, and total) as well as listed. Percentages will be based on number of participants in the safety population.

6.11 Pooled Placebo

Participants in the placebo group will be pooled across study Parts for summaries and comparison to PLN-74809 treatment groups.

6.12 Baseline and Clinical Characteristics

Baseline summaries will be presented by treatment group (PLN-74809 dose (40, 80, 160 or 320 mg, All PLN-74809) or Placebo) and overall (PLN-74809 dose and Placebo) for the following variables based on the safety population:

Demographic Data

- Age at informed consent (years)
- Sex
- Ethnicity
- Race, where more than 1 race is selected the participant will be presented under the 'Multiple races' category in the summary but each selected race will be displayed in the listing.

Baseline Characteristics

- Weight at Screening (kg)
- Height at Screening (cm)
- BMI at Screening (kg/m^2)
- Fertility status (childbearing potential, postmenopausal, surgically sterile)

Clinical Characteristics

- Duration since diagnosis at baseline (defined as the number of months from start date of first date reported for medical history preferred term "Cholangitis sclerosing" to first dose)
- Use of UDCA (Yes/no)
- Duration of UDCA usage at baseline (defined as the number of months from start date of UDCA to first dose)
- Partial Mayo Score for IBD (for participants with IBD ongoing at screening)
- [redacted]

6.13 Medical History

Separate tabulations of prior and ongoing conditions at screening will be presented by treatment group and overall for the safety population. All reported medical history data will be listed. Nonpharmacological procedures will be provided as a separate listing.

6.14 Prior and Concomitant Medications

Prior medications are defined as any medications taken prior to the first dose of study drug but stopping before the date of the first dose of study drug.

Concomitant medications are defined as medications taken on or after the date of the first dose of study drug or medications that were taken before the first dose of study drug and stopped after the first dose of study drug.

Prior and concomitant medications will be presented by ATC Level 4 classification and preferred name for each treatment group in the safety population.

All reported medications will be listed.

6.15 Exposure to Study Drug

Duration of exposure (in days) will be summarized by treatment group for the safety population.

6.16 Study Drug Compliance

Compliance (%) will be calculated for each participant and summarized by treatment group and overall. All compliance and study drug accountability data will be listed.

6.17 Pharmacokinetic Analyses

Blood samples for determination of plasma concentrations of PLN-74809 will be obtained [redacted] after administration of study drug [redacted]

Concentration data will be obtained for PLN-74809 [redacted]

PLN-74809 concentration data [redacted] will be summarized by dose level and visit at each scheduled sample time (nominal time) using descriptive statistics. Line plots will also be provided showing mean (SD) by visit. [redacted] Concentrations that are below the limit of quantification (BLQ) will be set to 0 for summary statistics. BLQ concentrations will be retained as BLQ in listings. The data will be reported to 3 significant figures.

Individual PLN-74809 concentration data [redacted] will be provided in listings. Data may be pooled with data from other studies for population PK and reported outside of the clinical study report.

6.18 Pharmacodynamic Analyses

Biomarker analyses will be presented by treatment group for the PD Analysis Population per Table 1.

Table 1. PSC Biomarkers

Biomarker	Timepoints (Parts 1 and 2)	Timepoints (Part 3)
PRO-C3 [redacted]	Baseline, Weeks 2, 4, 8, 12 and Week 16 (off-treatment)	Baseline, Weeks 2, 4, 8, 12, 24, EOT (variable weeks) and EOS (variable weeks)
ELF [redacted]	Baseline, Weeks 4 and 12	Baseline, Weeks 4, 12 and 24
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
ALP, [redacted]	Baseline, Weeks 2, 4, 8, 12 and Week 16 (off-treatment)	Baseline, Weeks 2, 4, 8, 12, 18, 24, 32, 40, 48 and 52 (off treatment)

[redacted]

Biomarker results obtained from plasma, or serum samples will be summarized using descriptive statistics by treatment group and visit for each parameter. Actual biomarker concentration at each visit, the absolute change from baseline and relative change (percentage change) from baseline will be presented. [redacted]

[redacted]

- [redacted]

If provided, the result adjusted for dilution factor will be used in summaries and listings. Any samples hemolyzed, received ambient, or with a note indicating improper storage will be excluded from summaries and listed only. If a sample has been excluded, then the change from baseline for that sample will also not be calculated.

6.18.1 Biomarkers with One Post Baseline Assessment

The following endpoints include only one post baseline assessment for Parts 1, 2 and 3 Week 12 interim analysis:

- [redacted]

Endpoints measured at baseline and only one post baseline visit will be analyzed by the analysis of covariance (ANCOVA). [redacted] The LS means, corresponding SEs, and 95% CI for each treatment group will be obtained from the model. An estimate for the LS mean difference (PLN-74809 vs. placebo), corresponding SE, 95% CI, and p-value for each dose group will also be presented. Each individual active group will be compared to pooled placebo (Parts 1, 2 and 3). [redacted]

Actual biomarker concentrations will be presented as a box plot by treatment group for each parameter. In addition, line plots using the LS estimated values and corresponding SE will also be presented.

6.18.2 Biomarkers with 2 or more Post Baseline Assessments

The following endpoints include at least two post baseline assessments:

- [redacted]
- Liver function parameters: ALP[redacted]
- Liver fibrosis parameters: PRO-[redacted]
- [redacted]

Endpoints measured at baseline and at least two post baseline visits will be analyzed using a mixed-effect model repeated measures (MMRM) [redacted]

The LS means, corresponding SEs, and 95% CI for each treatment group at each visit will be obtained from the model. An estimate for the LS mean difference (PLN-74809 vs. placebo), corresponding SE, 95% CI, and p-value for each dose group at each visit will also be presented. Each individual active group will be compared to pooled placebo (Parts 1, 2 and 3). [redacted]

[redacted]

For biomarkers with at least 2 postbaseline scheduled assessments, LS Mean change from baseline will be presented as a line plot showing baseline (0) and the LS mean (±SE) concentration at each post-dose visit by treatment group for each parameter.

[redacted]

6.19 Exploratory and Additional Analyses

Exploratory analyses will be presented by treatment group for the safety population. Tabulations and figures will be presented overall [redacted]

6.19.1 Magnetic Resonance-based Liver Imaging

MR-based liver imaging will be performed at screening and Week 12 (Parts 1, 2, and 3) and at Week 24 (Part 3 only).

Descriptive statistics for observed values at baseline and postbaseline visits will be provided, along with the change from baseline to each postbaseline visit, tabulated by treatment group for the following endpoints:

- Whole liver gadoxetate MRI relative enhancement (RE)
- [redacted]

- Bile duct gadoxetate MRI time of arrival (unit: seconds)
- [redacted]

A comparison of each parameter (PLN-74809 vs. placebo) will be performed. P-values will be derived from t-tests using the following SAS code:

[redacted]

The comparison will be analyzed between each treatment and placebo for the observed values and change from baseline values at each visit.

6.19.2 Patient-Reported Outcomes

Questionnaires to assess PROs will be administered at baseline, Weeks 4 and 12 (Parts 1, 2, and 3), and at Week 24 (Part 3 only).

Descriptive statistics for observed values at baseline and postbaseline visits will be provided, along with the change from baseline to each postbaseline visit, tabulated by treatment group.

A comparison of each parameter change from baseline (PLN-74809 vs. placebo) will be performed. P-values will be derived from t-tests.

Tabulations and graphical summaries will be provided for the following PROs and associated subdomains (as appropriate):

- Partial Mayo Score for IBD [redacted]
- [redacted]

6.19.3 Ultrasound-based Transient Elastography (FibroScan®)

Each participant will undergo an ultrasound-based transient elastography (FibroScan®) assessment at screening and Week 12 (Parts 1, 2, and 3) and at Week 24 (Part 3 only).

Descriptive statistics for observed values at baseline and postbaseline visits will be provided, along with the change from baseline to each postbaseline visit, tabulated by treatment group.

A comparison of each parameter (PLN-74809 vs. placebo) will be performed. P-values will be derived from t-tests.

[redacted]

[redacted]

Safety Analyses

Safety analyses will be presented by the treatment received for the Safety Population.

6.20 Adverse Events

AE analyses will be presented by the actual treatment received for the Safety Population. [redacted]

AEs will be collected from the time of informed consent through completion of the participant's last study visit.

A treatment-emergent adverse event (TEAE) is defined as:

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

AEs occurring prior to first dose of study drug are considered non-treatment emergent and will be listed only.

The Investigator will determine the relationship of the AE to treatment (related, not related). If an AE has missing relationship it is assumed to be related to the study drug 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 (fatal). Grade 3 (severe) will be assumed for an AE with missing grade.

An overall summary of AEs (number of participants with an event) will be presented by treatment group and overall, for the following:

- TEAE

- TEAE related to study drug
- TEAE Related to a Study Procedure
- Serious TEAE
- Serious TEAE Related to Study Drug
- TEAE of CTCAE Grade 3 or Higher
- TEAE of CTCAE Grade 3 or Higher Related to Study Drug
- TEAE Leading to Interruption of Study Drug
- TEAE Leading to Withdrawal of Study Drug
- TEAE Leading to Early Termination from Study
- TEAE Leading to Death

Summaries of TEAEs (number of participants with an event) will be presented by system organ class and preferred term by treatment group for the following:

- TEAE
- TEAE Related to Study Drug
- Serious TEAE
- Serious TEAE Related to Study Drug
- TEAE Related to a Study Procedure
- TEAE of CTCAE Grade 3 or Higher
- TEAE of CTCAE Grade 3 or Higher Related to Study Drug
- TEAE Leading to Withdrawal of Study Drug
- TEAE by SOC, PT and Maximum Grade (incidence only)
- [redacted]

The following listings of TEAEs will be presented in Section 14.3.2 of the CSR.

- TEAE Leading to Withdrawal of Study Drug
- TEAE Leading to Early Termination from Study
- TEAE Leading to Death
- Serious TEAE

[redacted]

System organ class will be presented in descending order of frequency in the pooled PLN-74809 group and then alphabetically. Preferred terms will be displayed in descending order of frequency in the pooled PLN-74809 group and then alphabetically.

For summary by severity, participants reporting more than one AE per system organ class and preferred term will only be counted once for the most severe event.

[redacted]

[redacted]

[redacted]

6.20.2 Laboratory Data

Descriptive statistics of the observed values and change from baseline will be presented by treatment group and visit for each continuous hematology, serum chemistry, coagulation, and urinalysis parameter. Shift tables for the change from baseline in categorical parameters will presented in the natural order of the outcome where possible.

Summaries and listings will be presented using the Système International (SI) unit for each parameter as received from the analytical laboratory.

Each measurement (for continuous data where provided) will be classified as below, within, or above normal range based on ranges supplied by the laboratory used. Shift tables in relation to the normal range from baseline to each follow-up visit will be presented.

Clinical laboratory test parameters outside the reference ranges will be flagged. The incidence of treatment-emergent laboratory abnormalities (on or after first dose of study) will be summarized by severity and treatment group.

[redacted]

All individual laboratory data (including pregnancy testing data) will be listed.

6.20.3 Vital Signs

Descriptive statistics for observed values and changes from baseline in the following vital signs will be presented by treatment group at each visit:

- Systolic blood pressure (mmHg)
- Diastolic blood pressure (mmHg)
- Pulse rate (bpm)
- Body temperature (degrees Celsius)

All vital sign data will be listed.

[redacted]

6.20.5 Physical Examination

Abnormal findings in physical examination will be recorded as medical history for pre- dose assessments and as adverse events for post-dose assessments.

7 INTERIM ANALYSIS

Interim analyses, covering all planned final analyses up to the interim data cut date, will be conducted at the time points indicated below:

- Following full enrollment and completion of the 12-week treatment duration with 40, 80, or 160 mg PLN-74809 (completion of Parts 1 and 2).
- Following full enrollment and completion of the 12-week treatment duration with 320 mg PLN-74809 (Part 3)

[redacted]

Blinding measures for interim analyses performed on data up to Week 12 for all participants in Part 3 will be described in a separate blinding plan. Briefly, every effort will be taken to maintain the blind in the required blinded portion of the trial. The analysis and interpretation of interim results will be conducted by a separate unblinding team who are not involved in the ongoing study conduct. The blinding plan will describe the membership and level of data access of the unblinded and blinded teams and appropriate documentation process in the suspected unintentional unblinding of a blinded team member. Blinded team members will not have access to individual treatment assignment or individual study results. Aggregate results will be presented to Sponsor management.

Interim data from Part 3 will include all assessments up to the Week 12 assessments, [redacted]. Adverse events or concomitant medications started/initiated [redacted] will not be summarized in the in the interim analysis and will be presented in the final analysis. Participants who discontinue treatment or the study post the Week 12 assessment date [redacted] will be summarized as on treatment/on study for the purposes of the interim analyses.

8 DATA AND SAFETY MONITORING BOARD ANALYSIS

Data and safety monitoring board (DSMB) analyses [redacted] will be performed by an external vendor. All DSMB related reporting are detailed in the DSMB Charter.

9 CHANGES TO PLANNED PROTOCOL ANALYSIS

The following additions or revisions to protocol specified analyses are included in this SAP:

- Primary endpoint was clarified as treatment emergent adverse events versus adverse events.
- [redacted]
- Removal of the analysis of [redacted] after determination that [redacted] would provide limited utility.
- Removal of analysis of [redacted] after determination that biomarker would provide limited utility.
- Addition of [redacted] as an exploratory biomarker.
- [redacted]
- Clarification of which timepoints will be analysed for exploratory biomarkers based on pharmacodynamic sampling plan.

[redacted]

[redacted]

[redacted]

STATISTICAL ANALYSIS PLAN

[redacted]

[redacted]

[redacted]

[redacted]

STATISTICAL ANALYSIS PLAN

[redacted]

[redacted]

[redacted]

STATISTICAL ANALYSIS PLAN

[redacted]

STATISTICAL ANALYSIS PLAN

[redacted]