STATISTICAL ANALYSIS PLAN

CB8025-21838

The Effect of Hepatic Impairment on The Pharmacokinetics of Seladelpar: An Open-Label Study Following Oral Dosing of Seladelpar to Subjects with Primary Biliary Cholangitis (PBC) and Hepatic Impairment

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SPONSOR:
CymaBay Therapeutics, Inc.

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Approvals

I confirm that I have reviewed this document and agree with the content.

Approval		
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Glossary of Abbreviations

Abbreviation	Description
AE	adverse event
Ae	amount excreted in urine
Ae_{0-t}	cumulative urinary excretion from time zero to time t, calculated as the sum of the amounts excreted over each collection interval.
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AR	accumulation ratio, calculated as C_{max} on Day 28/C_{max} on Day 1 or AUC_{0-tau} on Day 28/AUC_{0-24} on Day 1
AST	aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
AUC_{0-24}	area under the concentration-time curve from time zero to 24 hours
AUC_{0-inf}	area under the concentration-time curve from time zero to infinity
AUC_{0-t}	area under the concentration-time curve from time zero to the last measurable concentration
AUC_{0-tau}	area under the concentration-time curve for one dosing interval (τ) at steady-state
BQL	below quantification level
CI	confidence interval
CL/F	apparent total body clearance
CL,ss /F	apparent total body clearance at steady state
CL_R	renal clearance
C_{max}	maximum observed plasma concentration
$C_{max, ss}$	maximum observed plasma concentration at steady state
C_{min}	minimum observed plasma concentration
$C_{min, ss}$	minimum observed plasma concentration at steady state
CP	Child-Pugh
C_{trough}	trough observed drug concentration
CV	coefficient of variation
e	base for natural logarithm
DB	direct bilirubin
ECG	electrocardiogram
eCRF	electronic case report form
F	F statistic for F test
Fe	percentage excreted in urine

Abbreviation	Description
Fe_{0-t}	fraction (% dose) excreted unchanged, calculated as (100% x Ae_{0-t}) / Dose
Fu	average fraction of unbound seladelpar
GGT	gamma-glutamyl transferase
HI	hepatic impairment
ICH	International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use
INR	international normalized ratio
K_{el}	elimination rate constant
ln	natural logarithm
max	maximum
MedDRA®	Medical Dictionary for Regulatory Activities
MELD	model for end-stage liver disease
min	minimum
n	number of observations
N/A	not applicable
PBC	primary biliary cholangitis
PHT	portal hypertension
PK	pharmacokinetic(s)
PT	preferred term
p-value	probability value
Rsq	adjusted R-squared value for regression estimation of K_{el}
SAP	statistical analysis plan
SD	standard deviation
SOC	system organ class
SOP	standard operating procedure
$T_{1/2\ el}$	terminal elimination half-life
TB	total bilirubin
TEAE	treatment-emergent adverse event
TFLs	tables, figures, and listings
T_{max}	time to reach maximum observed plasma concentration
$T_{max,\ ss}$	time to reach maximum observed plasma concentration at steady state
TMF	trial master file
unbound AUC_{0-inf}	area under the concentration-time curve of unbound seladelpar from time zero to infinity
unbound AUC_{0-t}	area under the concentration-time curve of unbound seladelpar from

Abbreviation	Description
	time zero to the last measurable concentration
unbound C_{max}	maximum observed plasma concentration of unbound seladelpar
Vz/F	apparent volume of distribution
Vz,ss /F	apparent volume of distribution at steady state
WHO DD	World Health Organization Drug Dictionary

1. Purpose

The purpose of this statistical analysis plan (SAP) is to ensure that the data listings, summary tables, and figures that will be produced, and the statistical methodologies that will be used, are complete and appropriate to allow valid conclusions regarding the study objectives.

This SAP is based on the following documents:

- Protocol No. CB8025-21838 version 5.0, dated 06 March 2023.
- Electronic Case Report Form (eCRF) version 2.00 dated 19-Sep-2022.

2. Study Objectives

- Primary objectives:
    - Evaluate the Pharmacokinetic (PK) profiles of seladelpar and major metabolites: M1, M2 and M3 after a single dose and multiple oral doses in primary biliary cholangitis (PBC) subjects with hepatic impairment (HI).
    - Evaluate the safety and tolerability of seladelpar after a single dose and multiple oral doses in PBC subjects with HI.
- Secondary objectives:
    - Evaluate the urinary PK of seladelpar and its major metabolites: M1, M2 and M3 in PBC subjects with HI.
    - Evaluate the relationship between plasma seladelpar PK parameters (C_{max}, AUC_{0-t} and AUC_{0-inf}) and albumin, bilirubin, prothrombin time, and Child-Pugh (CP) score.
- Exploratory Objectives:
    - Evaluate the effect of multiple dose treatment of seladelpar on biomarkers of cholestasis and liver function (Cohorts 2 and 3 only).

3. Study Design

3.1 Study Design and Population

This study is designed as a two-part open-label, non-randomized, single (Part A) and multiple (Part B) oral dose(s) of 10 mg seladelpar or less in PBC subjects with hepatic impairment (HI). HI is based on Child-Pugh (CP) classification (CP-A with and without portal hypertension [PHT], CP-B, or CP-C) and subjects are designated into the appropriate cohort by CP score.

At least 24 subjects are planned for enrollment in this study.

In Part A of the study, subjects are assigned to cohorts 1-4 based on CP classification. Number of subjects planned and dose levels are as follows:

Cohort Number	CP Classification	Number of Subjects Planned	Planned Dose
1	CP-A	6	10 mg

2	CP-A (+ PHT)	6	10 mg
3	CP-B	6	10 mg
4	CP-C	6 (2 sentinel, 4 non-sentinel)	10 mg*

* Dosing for the two sentinel subjects may be adjusted to a lower dose than 10 mg based on PK and safety data from Cohorts 1-3. Dosing for the remaining 4 non-sentinel subjects may be adjusted based on PK and safety data from the two sentinel subjects.

In Part B, subjects allocated to Cohort 2 and Cohort 3, who have completed Part A, will have a washout period of at least 14 days following last study drug administration in Part A and then receive individualized doses of seladelpar , under fasting conditions, for 28 consecutive days. The expected doses and dose regimen include 1-, 2-, 5- or 10-mg once a day or 1-, 2- or 5-mg once every other day.

Cohort Number	CP Classification	Number of Subjects	Planned Dose
2	CP-A (+ PHT)	6	Individualized
3	CP-B	6	Individualized

3.2 Determination of Sample Size

At least twenty-four subjects, male and/or female are planned for enrollment in the study in order to complete with at least six subjects per cohort. The sample size is based upon clinical considerations. Six subjects per cohort are expected to provide sufficient data to adequately assess the PK for seladelpar in populations with PBC and HI.

3.3 Subject Withdrawal and Replacement

Subjects may be withdrawn from the study for any of the following reasons:

- Study subject unable or unwilling to continue participation in the study.
- Adverse event (regardless of relationship to investigational product) that precludes further participation in the study in the judgment of the Investigator and/or Sponsor.
- Informed consent withdrawn.
- Lost to follow-up (after 3 documented attempts to contact the subject)
- The Investigator considers that it is in the best interest of the subject to discontinue participation in the study.
- Enrolled into the study in violation of this protocol.
- Female subjects who become pregnant
- Vomiting within 5 hours post-dose seladelpar
- CTCAE grade 3 or above possibly or probably related to study drug.
- At the discretion of the investigator for medical reasons.

- At the discretion of the Investigator or Sponsor for noncompliance.

See protocol Section 8.1.4 for additional information.

At the discretion of the Sponsor, subjects who withdraw, or are withdrawn, from the study may be replaced in order to complete the study with at least six subjects per cohort.

3.4 Timing of Analyses

3.4.1 Interim Analysis

An interim analysis, including PK, safety, and efficacy analyses may be performed on available data with the timing based on Sponsor decision.

3.4.2 Final Analysis

The final safety, tolerability, pharmacokinetic (PK), and efficacy analyses will take place after all subjects have completed the study.

4. Study Endpoints

4.1 Primary Endpoints

PK endpoints:

The PK parameters of seladelpar and major metabolites: M1, M2 and M3 after a single and multiple oral doses will be as follows:

- Plasma: C_{max}, T_{max}, $AUC_{0\text{-}t}$, $AUC_{0\text{-}inf}$, %extrap$AUC_{0\text{-}inf}$, $t_{1/2}$, K_{el}, Rsq, CL/F (seladelpar only), Vz/F (seladelpar only)
- Urine: Ae and $Ae_{0\text{-}t}$, Fe (seladelpar only) and $Fe_{0\text{-}t}$ (seladelpar only), and CL_R (seladelpar only)

Safety and tolerability endpoints:

The safety and tolerability outcome measures will be as follows:

- Type, frequency, severity, and relationship of TEAEs to seladelpar including the assessment of the following TEAEs of special interest (AESI): CTCAE Grade 2 increases in ALT, AST, bilirubin, CK, lipase, or sCr; and hepatic decompensation clinical events, including ascites, jaundice, esophageal variceal bleeding, and hepatic encephalopathy.
- Physical examination, 12-lead ECG and vital signs
- Biochemistry, hematology, coagulation, and urinalysis
- Efficacy (Part B, Cohorts 2 and 3 only): Change and relative change from baseline to Day 28 in ALP, GGT, ALT, AST, TB, DB, albumin and platelets

4.2 Secondary Endpoints

The PK parameters of unbound seladelpar will be as follows:

Plasma: unbound $AUC_{0\text{-}t}$, unbound $AUC_{0\text{-}inf}$, unbound C_{max}, and Fu

5. Analysis Sets

All subjects' inclusion status into each analysis set will be determined after database lock.

5.1 Enrolled Set

The enrolled set will include all enrolled subjects. The enrolled set will be used for subject listings.

5.2 Safety Analysis Set

The safety analysis set comprises all study subjects who receive any amount of seladelpar . This analysis set will be used for all analysis of safety data and for summarization of demographics and baseline characteristics.

5.3 PK Concentration Set

The PK concentration set will include subjects who received any amount of seladelpar and have at least one post-dose concentration. Subjects with an insufficient number of PK samples to derive PK parameters will still be used for listings of PK concentrations. This population set will be used for summarization of PK concentration data.

5.4 PK Analysis Set

The PK analysis set will consist of all study subjects who undergo PK sampling and have assay results and for whom the PK profile can be adequately characterized. This analysis set will be used for the PK analyses and for summarization of parameter data.

Any subject with a protocol deviation or AE deemed to affect PK may be excluded from the PK analysis set. Subjects may also be excluded from the PK analysis set based upon the following: inclusion and exclusion criteria, acceptable times for visit dates and measurements, compliance with treatment, the nature and quality of the data, withdrawal, and any protocol deviation (such as vomiting that occurs within 5 hours post-dose). The Investigator and/or the Sponsor will make the final decision of which subjects will be included in the PK analysis set.

5.5 Efficacy Analysis Set

The efficacy analysis set will consist of all study subjects who receive any amount of seladelpar in Part B and have at least one biochemistry assessment post Part B baseline. This analysis set will be used for analyzing efficacy parameters (Cohorts 2 and 3, Part B only). The Investigator and/or the Sponsor will make the final decision of which subjects will be included in the efficacy analysis set.

6. General Aspects for Statistical Analysis

Unless otherwise stated, the descriptions of the analyses that follow apply to all study parts.

6.1 General Methods

SAS for Windows software will be used to perform all data analyses. All data in the database will be presented in the data listings.

6.2 Summary Statistics

Unless otherwise stated, continuous variables in PK analyses will be summarized with the following descriptive statistics: number of observations (n), arithmetic and geometric means, standard deviation (SD), coefficient of variation [CV (%)), median, minimum (min) and maximum

(max), unless otherwise specified. Continuous variables in safety and efficacy analyses will be summarized with n, arithmetic means, SD, median, min and max, unless otherwise specified. The min and max values will be presented to the same number of decimal places as recorded in the eCRF, mean, geometric mean and median will be presented to one more decimal place than the raw data, and the SD will be presented to two more decimal places than the raw data.

Summaries of change-from-baseline variables will include only subjects who have both a baseline value and corresponding value at the timepoint of interest. Categorical variables will be summarized with frequency counts and percentages. Percentages will be rounded to one decimal place, with the denominator being the number of subjects in the relevant analysis set, unless otherwise stated.

For PK data, values will be rounded to two decimal digits in the listings and tables, except for the following situations:

- Terminal elimination rate constant (K_{el}) and adjusted R-squared value for regression estimation of K_{el} (Rsq) data shall be rounded off to four decimal digits.
- PK parameters related to time, such as time to reach maximum observed plasma concentration (T_{max}), must be reported with the same precision as the actual sampling time, rounded to three decimal digits.
- Concentration versus time data, as well as C_{max} shall be reported as they appear in the corresponding dataset.

Summary statistics, CV (%), will be presented in two decimal places. For calculated parameters, such as AUC, the rules of mean will follow those pre-specified, as displayed in listings for similar values (e.g., arithmetic mean T_{max} presented to three decimal digits and SD presented to four decimal digits).

Only data from protocol scheduled ("nominal") visits will be included in the summary tables. Data from unscheduled visits will not be included in the summary tables (unless they were used as baseline) but will be included in the listings and figures.

In the case of a repeated test, both assessments will be presented in the listings. If a repeat measurement was performed due to the first measurement being outside the normal range for the given assessment and the second assessment confirms the first measurement, then only the first measurement will be used for analysis and the second assessment will be considered an unscheduled timepoint. In the same case, if the second assessment falls within normal ranges, then the second assessment will be used for analysis of that timepoint. In all other cases, the first measurement will be taken as the assessment to be used for the analysis.

6.3 Key Definitions

Baseline:

Unless stated otherwise, baseline will be defined for each subject. For Part A, baseline will be defined as the last non-missing measurement (including repeated and unscheduled assessments) obtained prior to study drug administration in Part A. For Part B, baseline will be defined as the last non-missing measurement obtained prior to first study drug administration in Part B.

"Unknown", "Not Done", "Not Applicable" and other classifications of missing data will not be considered when calculating baseline observations, unless the finding is a valid categorical observation.

Study day:

Study day for Part A and Part B are specified separately. For Part A, study day will be calculated using first study drug administration date in Part A as the reference date. For Part B, the reference date is the first study drug administration date in Part B. If the date of interest occurs on or after the first study drug administration date, study day will be calculated as (date of interest – first study drug administration date) + 1. If the date of interest occurs prior to the first study drug administration date, study day will be calculated as (date of interest – first study drug administration date). There will be no study day 0.

6.4 Missing Data

There will be no imputation for missing data, unless otherwise specified. Missing data shall be presented in subject listings as either "-" (unknown or not evaluated) or "N/A" (not applicable), with the corresponding definition in the footnotes. Missing descriptive statistics, or probability values (p-values), which cannot be estimated shall be presented as "-".

For inclusion in concomitant medication and AE tables, incomplete start and stop dates on the eCRF will be imputed as follows:

- If the stop date is incomplete, the following rules will be applied:
    - Missing day: Assume the last day of the month.
    - Missing day and month: Assume the last day of the year.
    - Missing day, month, and year: Assume that the event/medication is continuing.
    - In the case of the death of a subject, and if the imputed end date is after the date of death, the end date will be imputed as the date of death.
- If the stop date is incomplete, the imputed end date will be used instead of the reported end date.
- If the start date is incomplete, the following rules will be applied:
    - Missing day: Assume the first day of the month; however, if the partial date and the date of first study drug administration lie within the same month and year and the date of first study drug administration is not after the stop date of the event/medication, set to the date of study drug administration. Otherwise, set to the stop date of the event/medication.
    - Missing day and month: Assume January 1st; however, if the partial date and the date of first study drug administration lie within the same year and the date of first study drug administration is not after the stop date of the event/medication, set to the date of first study drug administration. Otherwise, set them to stop date of the event/medication.

- Missing day, month, and year: Assume date of first study drug administration if it is not after the stop date for the event/medication. Otherwise, set them to stop date for the event/medication.

In the case of withdrawal of consent, all data from subjects who withdraw from the study will be included in all summaries up to the time of withdrawal. For all other withdrawals, all data captured will be included in the safety summaries.

For PK analysis, only observed concentration data will be used in the data analysis. No attempt will be made to extrapolate or interpolate estimates for missing data.

7. Subject Characteristics

7.1 Subject Disposition

The number of subjects who were screened, enrolled, who were dosed, who completed the study, and who were discontinued from the study, will be presented. The data will be summarized by study part, cohort, and overall (frequency and the percentage of subjects) and listed by subject. If applicable, reasons for discontinuation will also be listed by subject. The number of subjects in each analysis set will also be summarized by study part, cohort, and overall.

If subjects (in cohorts 2 and 3) completed the study, they completed both Part A and B. If subjects did not complete the study and discontinued before the Part A follow-up telephone call (Part A Day 7±1), they did not complete Part A and did not enroll in Part B. If subjects did not complete the study and discontinued after the Part A follow-up telephone call (Part A Day 7±1), they completed Part A but discontinued Part B.

7.2 Protocol Deviations

Subject data will be examined for evidence of protocol deviations. All protocol deviations will be categorized and listed by subject.

7.3 Inclusion and Exclusion Criteria

All recorded inclusion and exclusion criteria status will be presented in a data listing. Each subject's inclusion or exclusion will also be presented by study parts and cohorts in a data listing.

7.4 Demographics and Baseline Characteristics

All demographics and body measurements will be summarized by study part and cohort and listed by subject. If the safety analysis set and PK analysis set are different, then a separate table for the PK analysis set will be generated. The demographics characteristics include age (years), sex (male or female), childbearing potential if female, menopausal status if female, ethnicity, race. The baseline characteristics consist of height (cm), weight (kg), body mass index (BMI) (kg/m2), baseline CP score, baseline MELD score, and baseline selected laboratory parameters including AST, ALT, GGT, ALP, TB, DB, albumin, platelets and INR.

Descriptive statistics (n, mean, SD, min, median, and max) will be calculated for continuous variables using the last results obtained prior to study drug administration. Frequency counts and percentages will be tabulated for categorical variables for the safety analysis set.

7.5 Medical History

Medical history will be presented by cohort in a data listing. The Medical Dictionary for Regulatory Activities (MedDRA) will be used to classify all medical history findings by system organ class (SOC) and preferred term (PT). Medical history of subjects will be summarized using counts and percentages by cohort.

7.6 Medications

If medications stopped on or after first study drug administration in Part A and before first study drug administration in Part B, they are concomitant medications for Part A. If medications were taken from before first study drug administration in Part B and stopped on or after first study drug administration in Part B, they are concomitant medication in both Part A and B. If medications were taken on or after first study drug administration in Part B, they are concomitant medications in Part B. Prior medications are medications stopped prior to first study drug administration in Part A. Prior and concomitant medications will be coded using the latest version of the World Health Organization Drug Dictionary (WHO DD) and be presented in a data listing. The total number of concomitant medications and the number and percentage of subjects with at least one concomitant medication will be summarized for the safety analysis set. Concomitant medication data will be presented separately by study part, cohort, anatomical therapeutic chemical (ATC) classification code (2nd level), and PT. When 2nd level classification code is not available, 1st level classification will be used instead.

7.7 Concomitant procedures

A concomitant procedure is any therapeutic intervention (e.g., surgery, biopsy, physical therapy) or diagnostic assessment (e.g., blood gas measurement, bacterial cultures) performed during subjects' participation during the study. Concomitant procedures will be listed by subject, study part and cohort.

7.8 Urine Drug Screening

Urine drug screen: Amphetamine, barbiturates, benzodiazepines, cocaine, ecstasy (MDMA), methadone, opiates, oxycodone, phencyclidine (PCP), propoxyphene, tricyclic anti-depressants (TCA). Cannabinoids are not included in this drug screen.

The results of the drug screen will be presented in a data listing.

7.9 Pregnancy Screening

The results of pregnancy tests will be presented in a data listing.

7.10 Additional Screening Tests

The results of serology tests, CP assessments, genotyping tests, and COVID-19 tests will be presented in data listings.

No data analysis or summary tables will be generated for the above.

8. PK Analyses

8.1 Data Presentation

For all PK analyses, concentration values below the quantification level (BQL) will be set to

"0.00". No imputations will be made on BQL concentrations. For listings, it will be listed as 'BQL'.

Invalid concentration values (due to bioanalytical or clinical issues) that occur prior to dosing will be replaced by "0.00". Invalid concentration values that occur after dosing will be set to "missing" for tabulation, graphical representation, and calculation purposes.

The actual clock time for dosing and the actual clock time for each PK sample collection will be recorded. For all sampling times, the actual sampling duration will be calculated as the difference between the sample collection actual clock time and the actual clock time of dosing. The actual post-dose sampling times, expressed in hours and rounded off to three significant digits, will be used to calculate the PK parameters. Pre-dose sampling times will always be reported as zero (0.000), regardless of the time difference. Nominal sampling times will be used in concentration tables and mean graphs, while actual sampling times for post-dose samples will be used in the individual graphs. Actual sampling times for post-dose samples also will be used for plasma PK parameter derivation, unless the actual sampling time is missing, in which case, the nominal time will be used. For urine PK parameters, nominal times will be used.

8.2 PK Sampling Schedule

Blood samples for PK analysis of will be drawn according to the following schedule:

Part A:

Blood samples for plasma PK of seladelpar and metabolites M1, M2 and M3 will be obtained at the following times:

- Day 1: pre-dose sample (≈ 10 minutes before seladelpar administration), ±5 minutes for 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, and 5 hours post-dose, and ±10 minutes for 6, 8 and 12 hours post-dose, ±15 minutes for 24 hours post-dose and ±30 min for 48 and 72 hours post-dose.

Blood samples for plasma PK of unbound seladelpar will be obtained at the following times:

- Day 1: ±5 minutes for 2.5 hours post-dose, and ±10 minutes for 12 hours post-dose.

Urine samples for PK analysis will be collected at the following times:

- Day 1: For urine collection, subjects will be instructed to empty their bladder before seladelpar administration. Urine will be collected over the following intervals: pre-dose (spot) and 0-6 hours, and 6-12 hours.

Part B:

Blood samples will be taken on:

- Day 1: pre-dose and 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 12, and (Day 2 pre-dose) 24 hours post-dose
- Day 28: pre-dose and 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 12, 24 (Day 29), 48 (Day 30) and 72 hours post-dose (Day 31).
- Day 7 and Day 14: Pre-dose.

Plasma seladelpar and its major metabolites M1, M2, and M3 concentrations, collection times, and collection time deviations will be listed for the PK Population by study part and cohort for

all enrolled subjects. Plasma concentration and urine data for seladelpar and its major metabolites M1, M2, and M3 will be summarized for the PK concentration set by study part, cohort, and time point, dose regimen and visit (if applicable) using descriptive statistics (n, arithmetic mean, SD, CV %, geometric mean, minimum, median, and maximum). The individual and mean (±SD) plasma concentrations for seladelpar and its major metabolites M1, M2, and M3 will be presented graphically on both linear and semi-logarithmic scales by study part, cohort, dose regimen and visit (if applicable) for PK concentration set.

8.3 PK Parameters

All PK parameters will be presented in data listings and summarized in tables by analyte, study part, cohort, dose regimen and visit (if applicable) using descriptive statistics (n, arithmetic and geometric means, SD, CV (%), min, max, and median) for PK analysis set.

For Part A, the following PK parameters will be calculated, whenever possible, by standard non-compartmental methods for seladelpar and metabolites M1, M2 and M3.

Parameter	**Definition**
Plasma PK Parameter	
C_{max}	maximum observed plasma concentration
T_{max}	time to reach maximum observed plasma concentration
AUC_{0-t}	area under the concentration--time curve from time zero to the last measurable concentration
AUC_{0-inf}	area under the concentration--time curve from time zero extrapolated to infinity, calculated as $AUC_{0-t}+C_t/K_{el}$, where: C_t = the last measurable concentration.
%extrapAUC_{0-inf}	percentage area under the concentration-time curve from time 0 to infinity that is extrapolated
$T_{1/2}$	terminal elimination half--life, calculated as ln (2)/K_{el}
K_{el}	elimination rate constant
Rsq	adjusted R-squared value for regression estimation of K_{el}
CL/F*	apparent total body clearance, calculated as Dose/AUC_{0-inf}
Vz/F*	apparent volume of distribution, calculated as Dose/ AUC_{0-inf}*K_{el}
unbound AUC_{0-t}*	area under the concentration--time curve of unbound seladelpar from time zero to the last measurable concentration, calculated as Fu * AUC_{0-t}
unbound AUC_{0-inf}*	area under the concentration--time curve of unbound seladelpar from time zero to infinity, calculated as Fu * AUC_{0-inf}
unbound C_{max}*	maximum observed plasma concentration of unbound seladelpar , calculated as Fu * C_{max}
Fu*	average fraction of unbound seladelpar , calculated as the average of the values obtained at 2.50 and 12.0 h post-dose.
Urine PK Parameter	

Parameter	Definition
Ae	amount excreted in urine over a single collection interval
Ae_{0-t}	Cumulative urinary excretion from time zero to time t, calculated as the sum of the amounts excreted over each collection interval.
CL_R*	renal clearance, calculated as Ae_{0-t} / $AUC_{0-12.}$
Fe*	percentage excreted in urine over a single collection interval.
Fe_{0-t}*	Fraction (% dose) excreted unchanged, calculated as (100% x Ae_{0-t}) / Dose.

*seladelpar only

For Part B, the following PK parameters will be calculated, whenever possible, by standard noncompartmental methods for seladelpar and metabolites M1, M2 and M3.

Day 1, 24-hour Collection (Days 1 & 2):

Parameter	Definition
C_{max}	maximum observed plasma concentration
T_{max}	time to reach maximum observed plasma concentration
AUC_{0-t}	area under the concentration--time curve from time zero to the last measurable concentration
AUC_{0-24}	area under the concentration--time curve from time zero to 24 hours
AUC_{0-inf}	area under the concentration--time curve from time zero extrapolated to infinity, calculated as $AUC_{0-t}+C_t/K_{el}$, where: C_t = the last measurable concentration.
$T_{1/2}$	terminal elimination half-life, calculated as ln (2)/K_{el}
K_{el}	elimination rate constant
Rsq	adjusted R-squared value for regression estimation of K_{el}
CL/F*	apparent total body clearance, calculated as Dose/AUC_{0-inf}
Vz/F*	apparent volume of distribution, calculated as Dose/ AUC_{0-inf}*K_{el}

*seladelpar only

Day 7 & 14, Pre-dose:

Sample Matrix	Parameter	Definition
Plasma	C_{trough}	Trough observed drug concentration [measured concentration at predose of Days 7 & 14 (taken directly before next administration)]

Day 28, 72-hour Collection (Days 28, 29, 30 and 31):

Parameter	Definition
$C_{max, ss}$	steady-state maximum observed plasma concentration
$C_{min, ss}$	steady-state minimum observed plasma concentration
$T_{max, ss}$	steady-state time to reach maximum observed plasma concentration
AUC_{0-t}	area under the concentration--time curve from time zero to the last measurable concentration
AUC_{0-24}	area under the concentration-time curve from time zero to 24 hours
AUC_{0-tau}	area under the concentration-time curve for one dosing interval (τ) at steady-state. tau should be 24 hr for subjects with dose once a day and 48 hr for subjects with dose once every other day.
$T_{1/2}$	terminal elimination half—life, calculated as ln (2)/K_{el}
K_{el}	elimination rate constant
Rsq	adjusted R-squared value for regression estimation of K_{el}
CL,ss/F*	apparent total body clearance, calculated as Dose/AUC_{0-tau}
Vz,ss/F*	apparent volume of distribution, calculated as Dose/ AUC_{0-tau}*K_{el}
RC_{max}	Accumulation ratio based on C_{max}, Calculated as C_{max} on Day 28/ Day 1
$RAUC_{0-t}$	Accumulation ratio based on AUC_{0-t}, Calculated as AUC_{0-tau} on Day 28/ AUC_{0-24} on Day 1 for subjects with dose once a day and AUC_{0-tau} on Day 28/ AUC_{0-48} on Day 1 for subjects with dose once every other day.

*seladelpar only

Area under the concentration curve (AUC) parameters will be calculated using the linear trapezoidal method (linear up log down).

K_{el} will be estimated (by linear regression) from the slope of the terminal log-linear portion of the concentration versus time curve. This parameter will be the negative of the estimated slope of the linear regression of the ln-transformed concentration versus time profile in the terminal elimination phase. The best fit method will be used to calculate the K_{el} from at least three concentration data points, excluding C_{max}. Rsq must be ≥ 0.8.

8.4 Cohort Comparisons

A comparison of C_{max} , AUC0-t, and AUC0-inf for Cohort 2, Cohort 3, and Cohort 4 vs. Cohort 1 (reference cohort), will be undertaken for single dose for Part A. The estimated ratio of model-adjusted geometric means will be used to perform the comparisons.

To estimate the geometric mean ratio, a linear model will be fit to the data, per parameter (including only the data from the two cohorts being compared). The response variable will be the natural-log transformed PK parameter, and the model will include cohort as a fixed effect. The model will be fit using restricted maximum likelihood, and the Kenward-Roger degrees of freedom approximation. The form of the model is as follows:

$\ln(\text{PK Parameter}) = \mu + \text{cohort} + \epsilon$

Here, μ represents the overall mean, cohort is a fixed effect with two factors, and ϵ represents the associated model error.

From this model, the adjusted means will be estimated for each cohort. The difference in means will be estimated for each cohort comparison, accompanied by a corresponding (two--sided) 90% confidence interval (CI). The point estimates and confidence endpoints will be exponentiated using base e to obtain a point and interval estimate for the ratio of geometric means (presented to three significant digits). These transformed CI will indicate the degree of similarity among PK levels across each cohort pair. If the transformed CI is entirely contained within the margin (80% - 125%), then PK similarity may be concluded.

The SAS code to fit the model will follow the format below (using the Mixed Procedure). The input variables, datasets, and labels are depicted in italicized red text and have been given generic names.

```
proc mixed data = dataset order = data;
  class cohort (ref = 'Cohort 1') ;
  model ln_PK_parameter = cohort / ddfm = kr solution;

  lsmeans cohort;
  estimate ' Cohort 2 vs Cohort 1 ' cohort 1 -1 / cl alpha = 0.1;
  /* etc… */
  ods output estimates = estimates tests3 = tests covparms = covparms;
run;
```

Additionally, a non-parametric assessment to test for differences between each cohort (Cohort 2, Cohort 3, and Cohort 4) v.s. Cohort 1 (reference cohort) will be performed for Tmax for single dose for Part A by using the Wilcoxon rank-sum test. The point estimates and 90% CIs for the median difference of Tmax between each cohort and cohort 1 (Cohort 2 vs 1, Cohort 3 vs 1, and Cohort 4 vs 1) will be evaluated separately by using Hodges-Lehmann method.

The SAS code to perform the test will follow the format below (using the Npar1way Procedure). The input variables, datasets, and labels are depicted in italicized red text and have been given generic names.

```
proc npar1way data=dataset wilcoxon hl alpha=0.1;
  class cohort;
  var Tmax;
  exact wilcoxon hl;
  ods select WilcoxonScores HodgesLehmann;

run;
```

8.5 Analysis of Correlation

The correlation between plasma seladelpar PK parameters C_{max}, $AUC_{0\text{-}t}$, and $AUC_{0\text{-}inf}$ and albumin, bilirubin, prothrombin time, and CP score at baseline will be presented by scatter plots for Part A and Part B as follows:

- Scatter plots of PK param (C_{max}, $AUC_{0\text{-}t}$, or $AUC_{0\text{-}inf}$) vs. baseline albumin by study part,

cohort, dose regimen and visit (if applicable).

- Scatter plots of PK param (C_{max}, AUC_{0-t}, or AUC_{0-inf}) vs. baseline bilirubin by study part, cohort, dose regimen and visit (if applicable).
- Scatter plots of PK param (C_{max}, AUC_{0-t}, or AUC_{0-inf}) vs. baseline prothrombin time by study part, cohort, dose regimen and visit (if applicable).
- Scatter plots of PK param (C_{max}, AUC_{0-t}, or AUC_{0-inf}) vs. CP score for overall by study part, dose regimen and visit (if applicable).

9. Efficacy Analyses (Part B)

All efficacy data will be listed by subject and summarized by cohort and scheduled visit for the efficacy analysis set. The effect of multiple dose treatment with seladelpar on biomarkers of cholestasis and liver function will be presented using descriptive statistics (n, arithmetic means, SD, min, max, and median).

Observed values, changes from baseline and percentage change from baseline of efficacy parameters will be presented by cohort. Efficacy parameters include alkaline phosphatase (ALP), gamma-glutamyl transferase (GGT), total bilirubin (TB), direct bilirubin (DB), alanine aminotransferase (ALT), aspartate amino transferase (AST), albumin and platelets.

10. Safety

Safety and tolerability analysis will be performed for all subjects in the safety set. No inferential statistical analysis of safety data is planned.

10.1 Exposure

Study drug administration will be listed by subject.

10.2 Adverse Events (AEs)

AEs will be coded using MedDRA. AEs will be grouped by SOC and PT and summarized by study part and cohort. The summary tables will present the number and percentage of total subjects and number of events by SOC and by PT.

All AE summaries will be restricted to treatment-emergent adverse events (TEAEs) only. For Part A, TEAEs are defined as AEs that commence or worsen on or after the time of study drug administration in Part A until up to 30 days after study drug administration in Part A or before the first study drug administration in Part B (whichever is earlier). For Part B, TEAEs are defined as AEs that commence or worsen on or after the time of first study drug administration in Part B until up to 30 days after the last study drug administration in Part B. AEs without an onset date or time, or AEs with an onset date of the date of first study drug administration but without an onset time, will be defined as treatment-emergent, unless an incomplete date (e.g., month and year) clearly indicates that the event started prior to administration of first study drug, or the AE stop date indicates that the event started and stopped prior to administration of first study drug. A drug-related TEAE is defined as TEAE which was related (reported as ‘possible’, ‘probable’, or ‘definite’) to study drug.

TEAEs will be summarized by study part and cohort. The number and percentage of subjects

experiencing TEAEs and the number of TEAEs will be tabulated. Subjects who experience the same AE (in terms of MedDRA PT) more than once will only be counted once per study part and cohort, however, the total number of events will be counted per category. This also applies to sub-categories displayed in the summaries.

The following summaries will be presented:

- Overall summary of TEAEs
- TEAEs by SOC and PT
- TEAEs by PT.
- TEAEs by PT, and severity.
- TEAEs by PT, and relationship to study drug.
- Serious TEAEs by PT.
- Drug-related TEAEs by PT.
- Drug-related serious TEAEs by PT.
- TEAEs leading to study discontinuation by PT.
- TEAEs leading to death.
- Liver-related TEAEs (Appendix 15.1).
- Muscle-related TEAEs (Appendix 15.2).
- Renal-related TEAEs (Appendix 15.3).
- Pancreatic-related TEAEs (Appendix 15.4).

All AEs will be listed. The following listings will be included: Non-TEAEs, TEAEs, and Serious TEAEs.

10.3 Clinical Laboratory Evaluations

Clinical laboratory data, including biochemistry, hematology, coagulation, and urinalysis, will be listed by subject and summarized by study part, cohort and scheduled visit. For all continuous laboratory variables, observed values and changes from baseline will be presented. For categorical laboratory variables, number and percentage of subjects by each category will be presented. Abnormal results will be flagged in the listings as “clinically significant” or “not clinically significant” per Investigator determination. Values outside of the laboratory's reference range (i.e., those with low or high values) will also be flagged in the listings. For all continuous laboratory variables, a shift table tabulating number and percentage of subjects with CTCAE grade (according to NCI CTCAE version 5.0 or the most recent version) changes from baseline to most extreme grade post baseline will be provided by study part and cohort. For laboratory parameters that are not gradable by the CTCAE, a shift table comparing the baseline value relative to the normal reference range (normal, low, and high) to worst postbaseline results will be presented by study part and cohort. For categorical variables of urinalysis, a shift table comparing the baseline value

to the maximum value will be presented by study part and cohort (number of subjects with results of normal, abnormal NCS and abnormal CS). In addition, subject incidence of elevated ALT, ALP, AST, bilirubin, CK, lipase and sCr with CTCAE Grade 2 or above will be summarized by study part, cohort, and scheduled visit.

The eGFR will be calculated using the following MDRD equation:

eGFR (mL/min/1.73 m^2) =

$$175 \times (S_{cr,\,std})^{-1.154} \times (Age)^{-0.203} \times (0.742 if\ female) \times (1.212 if\ AfricanAmerican)$$

where, $S_{cr,std}$ = serum creatinine in mg/dL measured with a standardized assay.

10.4 Vital Signs

Vital sign measurements will be listed by subject and summarized by study part, cohort and scheduled visit. Observed values and changes from baseline will be presented. Abnormal results as identified in Table 1 and Table 2 will be flagged in the listings.

Table 1 Vital Sign Values of Potential Clinical Concern

Vital Sign Parameter	Unit	Clinical Concern Range	
		Lower	Upper
Systolic Blood Pressure	mmHg	< 85	>160
Diastolic Blood Pressure	mmHg	< 45	> 100
Heart Rate	mmHg	< 40	> 110

Table 2 Vital Sign Changes from Baseline of Potential Clinical Concern

Vital Sign Parameter	Unit	Clinical Concern Range	
		Decrease	Increase
Systolic Blood Pressure	mmHg	≥ 40	≥ 40
Diastolic Blood Pressure	mmHg	≥ 20	≥ 20
Heart Rate	mmHg	≥ 30	≥ 20

10.5 Electrocardiograms (ECGs)

ECG values including heart rate, ventricular rate, PR interval, QRS duration, QT interval (uncorrected), and QTcF interval will be listed by subject and summarized by study part and cohort. Observed values and changes from baseline will be presented. Abnormal results will be flagged in the listings and marked as abnormal NCS or abnormal CS. A listing of subjects who have investigator-identified ECG abnormalities will be presented. Frequency counts and percentage of subjects as normal or abnormal (summarized by clinically significant or not clinically significant) ECG will be summarized by study part and cohort.

In addition, a shift table representing the categorical change in overall interpretation (normal, abnormal not clinically significant, or abnormal clinically significant) from baseline to each post baseline visit will be presented.

A categorical summary of abnormal QTcF values will be presented by the treatment group. The number of subjects with postbaseline values of ≥450 msec, ≥480 msec, and ≥500 msec will be presented, and the number of subjects with change from baseline values of ≥30 msec and ≥60 msec will also be presented. The postbaseline period of ECGs is up to the earliest of 1) subject last contact date; 2) 30 days after the last study dose date; 3) first seladelpar dose in the next study those subjects enrolled into, if applicable.

10.6 Physical Examination

The results of physical examinations will be listed by subject, study part and cohort. Abnormal results will be flagged in the listings.

11. Changes from Analysis Planned in the Protocol

The protocol defined a TEAE category of Adverse Events of Special Interest (AESI) as AEs that meet CTCAE Grade 2 criteria or higher for AEs of elevated ALT, AST, bilirubin, CK, lipase, or sCr; hepatic decompensation clinical events including ascites, jaundice, esophageal variceal bleeding, and hepatic encephalopathy were also defined as AESIs. For clarity in data reporting, laboratory findings will be summarized and reported based on laboratory values directly and abnormalities will not be reclassified as AEs (see Section 10.3 for details on clinical laboratory summaries). The laboratory summary will include subject incidence of elevated ALT, AST, bilirubin, CK, lipase and sCr with CTCAE Grade 2 or above, summarized by study part, cohort, and scheduled visit. Adverse events summaries will include all TEAEs as defined by the protocol. To align with other seladelpar studies, this SAP defined AEs of interest as those reflecting potential liver, muscle, renal, or pancreatic toxicity. Events in these categories (which would include hepatic decompensation events) will be summarized for this study (see Section 10.2 for details on AE summaries).

The protocol defined efficacy analyses as a part of the safety and tolerability measures within the primary measures. To align with the stated study objectives, the efficacy analyses for multiple doses of seladelpar in the study were treated as exploratory analyses and measures.

12. Programming Considerations

All TFLs and statistical analyses will be generated using SAS for Windows, release 9.4 (SAS Institute Inc., Cary, NC, USA) software in accordance with Food and Drug Administration (FDA) guidelines. PK parameters calculations will be performed using a validated SAS macro

developed by Pharmax Research Inc.

12.1 General Considerations

- One SAS program can create several outputs.
- Each output will be stored in a separate file.
- Output files will be delivered in rich text format that can be manipulated in MS Word.
- Numbering of TFLs will follow International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) guideline E3. Table, Listing, and Figure Format

12.1.1 General

- TFLs will be produced in landscape format. The orientation may be changed to portrait, as necessary to allow additional rows to be presented.
- TFLs will be produced using the Times New Roman font, size 10. The font size may be reduced as necessary to allow additional columns to be presented, but not at the expense of clarity.
- The data displays for all TFLs will have a minimum blank 1-inch margin on all four sides.
- Unless otherwise specified, TFLs will be in black and white (no color).
- Specialized text styles, such as bolding, italics, borders, shading, and superscripted and subscripted text, will not be used in the TFLs, unless otherwise specified. On some occasions, superscripts 1, 2, or 3 may be used; see below.
- Standard keyboard characters will be used in the TFLs. Special characters, such as non-printable control characters, printer-specific, or font-specific characters, will not be used. Hexadecimal-derived characters will be used, where possible, if they are appropriate to help display math symbols (e.g., μ). Certain subscripts and superscripts (e.g., cm^2, C_{max}) will be employed on a case-by-case basis.
- TFLs will be produced using sentence case, unless otherwise specified.

12.1.2 Headers and Footers

- Times New Roman font with size 10 will be used for TFL headers and footers.
- All outputs will have the following at the top left of each page: CymaBay Therapeutics, Inc. Protocol CB8025-21838.
- All outputs will have page x of y at the top or bottom right corner of each page. TFLs are individually paginated in relation to total length (i.e., the page number appears sequentially as page x of y, where y is the total number of pages in the output).
- The date and time the output was generated will appear, along with the program name, at the bottom of each page.

12.1.3 Display Titles

Each display title includes the appropriate designation ("Table", "Figure", or "Listing") and a numeral, along with a descriptive name (e.g., Table 10.1 Subject Disposition). ICH E3 numbering is strongly recommended, but Sponsor preferences are obtained for final determination. Display titles are left aligned, single spaced, and presented in title case. A solid line spanning the margins will separate display titles from column headings.

12.1.4 Column and Row Headings

- Column and row headings are presented in the title case, with the exception of complete sentences, which will be presented in sentence case.
- In efficacy tables, the variable (or characteristic) column will be on the far left, followed by the group columns and overall column (if applicable). P-values may be presented under the overall column or in a separate p-value column (if applicable). Within-group comparisons may have p-values presented in a row beneath the summary statistics for that group.
- Column and row headings will include "Unit" for numeric variables, as appropriate.
- Column and row headings will include the number of subjects in the analysis set for each group, presented as (N=xx). This is different from the 'n' used in descriptive statistics, which represents the number of observations.

12.1.5 Body of the Data Display

12.1.5.1 General Conventions

Data in columns of a table or listing are formatted as follows:

- Alphanumeric values are left aligned.
- Whole numbers (e.g., counts) are right aligned.
- Numbers containing fractional portions are decimal-aligned.

12.1.5.2 Table Conventions

- Units will be included where available.
- If the categories of a parameter are ordered, then all categories between the maximum and minimum category are presented in the table, even if n=0 for all groups in a given category that is between the minimum and maximum level for that parameter. See the example for the frequency distribution for symptom severity below.

Severity Rating	N
Severe	0
Moderate	8
Mild	3

- Where percentages are presented in these tables, 0% will not be presented, therefore, counts of zero will be presented as "0", not "0 (0%)".
- If the categories are not ordered (e.g., Medical History, Reasons for Discontinuation from

the Study, etc.), then only those categories for which there is at least one subject represented in one or more groups are included.

- An Unknown or Missing category is added to each parameter for which information is not available for one or more subjects.
- P-values are presented in the format: 0.xxx, where xxx is the value. Every p-value less than 0.001 will be presented as <0.001. If the p-value is less than 0.0001, then it is presented as <0.0001. If the p-value returns as >0.999, then it is presented as >0.999.
- Percentage values are presented in parentheses with no spaces, one space after the count [e.g., 7 (12.8%), 13 (5.4%)]. Predetermine how to display values that round down to 0.0. A common convention is to display as '<0.1', or as appropriate with additional decimal places. Unless otherwise noted, for all percentages, the number of subjects in the analysis set for the group that has an observation will be the denominator. Percentages after zero counts are not displayed, and percentages equating to 100% are presented as "100%" (without decimal places).
- Tabular display of data for medical history, prior/concomitant medications, and all tabular displays of adverse event data are presented in alphabetical order. Within the body system, ATC classification, and SOC, medical history (by PT), drugs (by ATC classification), and AEs (by PT) are displayed in alphabetical order.
- The percentage of subjects is normally calculated as a proportion of the number of subjects assessed in the relevant group (or overall) for the analysis set presented. However, careful consideration is required in many instances, due to the complicated nature of selecting the denominator, usually the appropriate number of subjects exposed. Details of this will be described in footnotes or programming notes.
- For categorical summaries (number and percentage of subjects) where a subject can be included in more than one category, describe in a footnote or programming note if the subject is included in the summary statistics for all relevant categories or just one category and the criteria for selecting the criteria.
- Where a category with a subheading (such as SOC) must be split over more than one page, present the subheading followed by "(cont.)" at the top of each subsequent page. The overall summary statistics for the subheading will only be presented on the first relevant page.

12.1.5.3 Listing Conventions

- Listings will be sorted for presentation in order of groups, as above, subject number, visit/collection day, and visit/collection time.
- Dates are printed in SAS DATE9.format ("ddMMMyyyy": 01JUL2000). Missing portions of dates are represented on subject listings as dashes (--JUL2000). Dates that are missing because they are not applicable for the subject are presented as "N/A", unless otherwise specified.
- All observed time values are to be presented using a 24-hour clock HH:MM or HH:MM:SS

format (e.g., 11:26:45, or 11:26). Time will only be reported if it was measured as part of the study.

- Units will be included where available.

12.1.5.4 Figure Conventions

- For safety figures, study visits will be displayed on the X-axis and endpoint (e.g., treatment mean change from baseline) values will be displayed on the Y-axis, unless otherwise specified.
- Legends will be used for all figures with more than one variable, group, or item displayed.
- Units will be included where available.

12.1.6 Footnotes

- A solid line spanning the margins will separate the body of the data display from the footnotes.
- All footnotes will be left aligned, with single spacing, immediately below the solid line beneath the data display.
- Informational footnotes begin with “Note:”. Reference footnotes begin with a reference number or letter (e.g., 1, 2, 3 or a, b, c).
- Each new footnote starts on a new line, where possible.
- Subject-specific footnotes are avoided, where possible.
- Footnotes will be used sparingly and add value to the table, figure, or data listing. If more than six lines of footnotes are planned, then a cover page may be used to display footnotes, and only those essential to comprehension of the data will be repeated on each page.

13. References

1. International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH). (1996). Guideline for Industry, Structure and Content of Clinical Study Reports (ICH E3).
2. CDER FDA Guidance for Industry Pharmacokinetics in Patients with Impaired Hepatic Function – Study Design, Data Analysis, and Impact on Dosing and Labeling – May 2003
3. Jones D, Boudes PF, Swain MG, et al. Seladelpar (MBX-8025), a selective PPARδ agonist, in patients with primary biliary cholangitis with an inadequate response to ursodeoxycholic acid: a double-blind, randomised, placebo-controlled, phase 2, proof-of-concept study. Lancet Gastroenterol Hepatol 2017;2(10):716-726.
4. Poupon RE, Lindor KD, Cauch-Dudek K, et al. Combined analysis of randomized controlled trials of ursodeoxycholic acid in primary biliary cirrhosis. Gastroenterology 1997; 113:884-890.

14. Appendices

14.1 Liver-related TEAEs

Liver-related TEAEs are defined using the broad Hepatic disorders SMQ (Standardized MedDRA Queries), with exclusion of those sub-SMQs: Congenital, familial, neonatal and genetic disorders of the liver; Liver infections; and Pregnancy-related hepatic disorders.

14.2 Muscle-related TEAEs

Muscle-related TEAEs are defined using the Myalgia FMQ (FDA Medical Queries) v2.1:

PT	Final Classification
Chest tenderness	Narrow
Eosinophilia myalgia syndrome	Narrow
Fibromyalgia	Narrow
Fibromyalgia syndrome	Narrow
Fibrositis	Narrow
Musculoskeletal discomfort	Narrow
Myalgia	Narrow
Myalgia aggravated	Narrow
Myalgia intercostal	Narrow
Neuromuscular pain	Narrow
Polymyalgia	Narrow
Polymyalgia aggravated	Narrow
Polymyalgia rheumatica	Narrow
Buttock pain	Broad
Chest wall pain	Broad
Costal pain	Broad
Cramp-fasciculation syndrome	Broad
Intercostal pain	Broad
Lupus myositis	Broad
Muscle spasms	Broad
Muscle tightness	Broad
Musculoskeletal chest pain	Broad
Musculoskeletal pain	Broad
Musculoskeletal stiffness	Broad
Myofascial pain syndrome	Broad
Myositis	Broad
Rhabdomyolysis	Broad
Shoulder blade pain	Broad
Myofibrillar myopathy	Broad
Pregnenolone deficiency	Broad

14.3 Renal-related TEAEs

Renal-related TEAEs are defined using the Acute renal failure SMQ (Standardised MedDRA Queries) v24.0.

PT	Scope	Category
Acute kidney injury	Narrow	A
Acute phosphate nephropathy	Narrow	A
Anuria	Narrow	A
Azotaemia	Narrow	A
Continuous haemodiafiltration	Narrow	A
Dialysis	Narrow	A
Foetal renal impairment	Narrow	A
Haemodialysis	Narrow	A
Haemofiltration	Narrow	A
Neonatal anuria	Narrow	A
Nephropathy toxic	Narrow	A
Oliguria	Narrow	A
Peritoneal dialysis	Narrow	A
Prerenal failure	Narrow	A
Renal failure	Narrow	A
Renal failure neonatal	Narrow	A
Renal impairment	Narrow	A
Renal impairment neonatal	Narrow	A
Subacute kidney injury	Narrow	A
Albuminuria	Broad	A
Blood creatinine abnormal	Broad	A
Blood creatinine increased	Broad	A
Blood urea abnormal	Broad	A
Blood urea increased	Broad	A
Blood urea nitrogen/creatinine ratio increased	Broad	A
Creatinine renal clearance abnormal	Broad	A
Creatinine renal clearance decreased	Broad	A
Creatinine urine abnormal	Broad	A
Creatinine urine decreased	Broad	A
Crystal nephropathy	Broad	A
Fractional excretion of sodium	Broad	A
Glomerular filtration rate abnormal	Broad	A
Glomerular filtration rate decreased	Broad	A
Hypercreatininaemia	Broad	A
Hyponatriuria	Broad	A
Intradialytic parenteral nutrition	Broad	A
Kidney injury molecule-1	Broad	A

Nephritis	Broad	A
Neutrophil gelatinase-associated lipocalin increased	Broad	A
Oedema due to renal disease	Broad	A
Protein urine present	Broad	A
Proteinuria	Broad	A
Renal function test abnormal	Broad	A
Renal transplant	Broad	A
Renal tubular disorder	Broad	A
Renal tubular dysfunction	Broad	A
Renal tubular injury	Broad	A
Renal tubular necrosis	Broad	A
Tubulointerstitial nephritis	Broad	A
Urea renal clearance decreased	Broad	A
Urine output decreased	Broad	A

14.4 Pancreatic-related TEAEs

Pancreatic-related TEAEs is defined using the Pancreatitis FMQ v1.0:

PT	Final Classification
Alcoholic pancreatitis	Narrow
Alcoholic pancreopathy	Narrow
Autoimmune pancreatitis	Narrow
Cytomegalovirus pancreatitis	Narrow
Haemorrhagic necrotic pancreatitis	Narrow
Ischaemic pancreatitis	Narrow
Lupus pancreatitis	Narrow
Obstructive pancreatitis	Narrow
Oedematous pancreatitis	Narrow
Pancreas infection	Narrow
Pancreatic abscess	Narrow
Pancreatic haemorrhage	Narrow
Pancreatic necrosis	Narrow
Pancreatic phlegmon	Narrow
Pancreatic pseudocyst	Narrow
Pancreatic pseudocyst drainage	Narrow
Pancreatitis	Narrow
Pancreatitis acute	Narrow
Pancreatitis bacterial	Narrow
Pancreatitis chronic	Narrow
Pancreatitis due to biliary obstruction	Narrow
Pancreatitis fungal	Narrow
Pancreatitis haemorrhagic	Narrow
Pancreatitis helminthic	Narrow
Pancreatitis necrotising	Narrow
Pancreatitis relapsing	Narrow
Pancreatitis viral	Narrow
Pancreatorenal syndrome	Narrow
Traumatic pancreatitis	Narrow
Amylase abnormal	Broad
Amylase increased	Broad
Blood amylase abnormal	Broad
Blood amylase increased	Broad
Blood trypsin increased	Broad
Cullen's sign	Broad
Grey Turner's sign	Broad
Hereditary pancreatitis	Broad
Hyperamylasaemia	Broad

Hyperlipasaemia	Broad
Lipase abnormal	Broad
Lipase increased	Broad
Lipase urine increased	Broad
Pancreatic enzyme abnormality	Broad
Pancreatic enzymes abnormal	Broad
Pancreatic enzymes increased	Broad
Peripancreatic fluid collection	Broad
Ultrasound pancreas abnormal	Broad