Statistical Analysis Plan

A Phase 1, Open-Label, Single-Dose Study to Investigate the Influence of Severe Hepatic Impairment on the Pharmacokinetics of Acalabrutinib and its Metabolite (ACP-5862)

Protocol No: ACE-HI-102
Final Protocol Date: 04 June 2018
Compound Name: Acalabrutinib (ACP-196)

Celerion Project CA24897
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Statistical Analysis Plan Signature Page

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Table of Contents

1. INTRODUCTION

The following statistical analysis plan (SAP) provides the framework for the summarization of the data from this study. The SAP may change due to unforeseen circumstances. Any changes made from the planned analysis within the protocol, after the locking of the database will be documented in the clinical study report (CSR). The section referred to as Table Shells within this SAP describes the traceability of the tables, figures, and listings (TFLs) back to the data. Note that the header for this page will be the one used for the main body of the CSR.

Any additional exploratory analyses not addressed within this statistical SAP and/or driven by the data, or requested by the sponsor, will be considered out of scope and must be described in the CSR.

2. OBJECTIVES AND ENDPOINTS

2.1 Objectives

Primary:

To compare the plasma pharmacokinetics (PK) of acalabrutinib and ACP-5862 in subjects with severe hepatic impairment (HI) with that in matched-control subjects following a single-dose administration of 50-mg acalabrutinib.

Secondary:

To evaluate the safety and tolerability of acalabrutinib in subjects with severe HI after a single-dose administration of 50-mg acalabrutinib.

Exploratory:

The exploratory objectives listed below may be investigated at the discretion of the sponsor:

- To determine the [redacted] of acalabrutinib and ACP-5862 in subjects with severe HI and matched-control subjects following a single 50-mg dose of acalabrutinib.
- To evaluate acalabrutinib and ACP-5862 [redacted] in subjects with severe HI and matched-control subjects following a single 50-mg dose of acalabrutinib.
- To assess the effect of acalabrutinib on [redacted] (eg, [redacted] and [redacted] in subjects with severe HI and matched-control subjects following a single 50-mg dose of acalabrutinib.

2.2 Endpoints

Pharmacokinetics:

The following PK parameters will be calculated for acalabrutinib and its metabolite, ACP-5862, in plasma, as appropriate: $AUC_{0\text{-last}}$, $AUC_{0\text{-inf}}$, $AUC_{0\text{-24}}$, $AUC_{\%extrap}$, C_{max}, T_{max}, T_{last}, λ_z, $t_{½}$, CL/F (parent only), V_z/F (parent only), metabolite-to-parent ratio (MR)_C_{max}, MR_$AUC_{0\text{-last}}$, and MR_$AUC_{0\text{-inf}}$.

Relationship between plasma acalabrutinib and ACP-5862 PK [redacted] and [redacted] may be investigated.

[redacted] of acalabrutinib and ACP-5862 in plasma will be determined at specified timepoints from blood samples collected for this purpose. Remaining PK blood samples may also be used to determine [redacted] of acalabrutinib and ACP-5862.

Remaining PK blood samples following analyses and dedicated [redacted] samples may be used for potential future analysis of [redacted] (eg, [redacted]).

Urine samples may be used for potential future analysis to estimate acalabrutinib and ACP-5862 [redacted] and analysis of [redacted] (eg, [redacted].

Safety:

Safety endpoints will include 12-lead ECGs, vital signs, clinical laboratory tests, adverse events (AEs), and physical examinations.

3. STUDY DESIGN

This is a Phase 1, non-randomized, open-label, single-dose study to evaluate the effect of severe HI on the PK of acalabrutinib and its major metabolite, ACP-5862.

A total of 16 adult men and/or women will be enrolled. Eight subjects with severe HI (a score of 10 to 15, on the Child-Pugh scale) will be enrolled to obtain at least 6 evaluable subjects. Not more than 25% of the hepatic-impaired subjects (eg, 2 of 8 subjects with HI) will be allowed to have a transjugular intrahepatic portosystemic shunt (TIPS).
Eight subjects with normal hepatic function to match all evaluable subjects with severe HI will be enrolled in a 1:1 ratio. Subjects will be matched for age [within age groups <45 years old or ≥45 years old], body weight [± 20 %], and sex [1:1] to the subjects with HI.

Screening of subjects will occur within 28 days before dosing.

On Day 1, a single oral dose of acalabrutinib will be administered followed by PK blood sampling for 24 hours in matched-control subjects and for 72 hours in subject with HI. Urine samples will also be collected over a 24-hour collection interval.

Safety will be monitored throughout the study by repeated clinical and laboratory evaluations.

Discontinued subjects may be replaced at the discretion of the sponsor.

Subjects will be housed on Day -1, at the time indicated by the clinical research unit (CRU), until after the 72-hour blood draw and/or study procedures for subjects with severe HI or until after the 24-hour blood draw and/or study procedures for matched-control subjects. At all times, a subject may be required to remain at the CRU for longer at the discretion of the PI or designee.

The CRU will attempt to contact all subjects who received the study drug (including subjects who terminate the study early) using their standard procedures approximately 14 days after dosing to determine whether any AE has occurred since the last study visit.

4. ANALYSIS POPULATIONS

4.1 Analysis Populations

Safety Population

The Safety Population will include all subjects who received the study drug.

Pharmacokinetic Population

The PK Population will include data from all subjects who received the study drug and display an evaluable PK profile (eg, exposure to treatment, availability of measurements and absence of major protocol violations).

All available data will be included in the concentration and PK parameter tables to the extent possible. Data for each subject will be included in the summary statistics and statistical comparisons of PK parameters with the exceptions described as follows:

- Data from subjects who experience emesis at or before 2 times the median Tmax for a given analyte (acalabrutinib or ACP-5862) during the PK sampling period time course of the study may be excluded from the summary statistics for the given analyte and from the statistical comparison of PK parameters if emesis occurs.
- Data from subjects who significantly violate a protocol inclusion or exclusion criteria, deviate significantly from the protocol, or have unavailable or incomplete data which may influence the PK analysis will be excluded from the PK analysis population.

Any subject or data excluded from the analysis will be identified, along with their reason for exclusion, in the CSR.

4.2 Preliminary Data and Interim Analysis

Celerion Biometrics will not perform interim analyses.

5. TREATMENT DESCRIPTIONS

Acalabrutinib will be supplied as 50-mg hard gelatin capsules.

Each subject will receive a single 50-mg acalabrutinib (1 x 50-mg capsules) dose to be administered orally with approximately 240 mL of water at Hour 0 on the morning of Day 1, after an overnight fast.

The treatment will be referred to in the text, tables and figures as a single oral dose of 50 mg acalabrutinib.

Subjects groups will be described based on the Child-Pugh classifications as follows in the treatment descriptions in the text, tables, figures, and listings:

Subject Group	Short Description	Long Description
(Column header)	(Text)	(footnotes, legends)
Group C	Severe HI	Severe Hepatic Impairment (Child-Pugh C)
Group N	Normal	Normal Hepatic Function (Healthy Control)

6. PHARMACOKINETIC ANALYSIS

6.1 Measurements and Collection Schedule

For all subjects, blood samples for the determination of acalabrutinib and ACP-5862 plasma concentrations will be collected at the following timepoints:

- Pre-dose and, 0.167, 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 14, 24, 36, 48, 60 and 72 hours post-dose in subjects with severe HI.
- Pre-dose and, 0.167, 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 14, and 24 hours post-dose in subjects with normal hepatic function.

Remaining PK blood samples following analyses may be used for potential future analysis of acalabrutinib and ACP-5862 [redacted] and [redacted]. Remaining dedicated protein binding samples may also be used for potential future analysis of [redacted].

Urine samples for determination of acalabrutinib and ACP-5862 will be collected at the following intervals: pre-dose, 0 to 4, 4 to 24 hours after dosing in subjects with severe HI and subjects with normal hepatic function.

All concentration data will be included in the calculation of the individual PK parameters, the individual concentration-time plots (based on actual sample times), and in the mean concentration-time plots (based on nominal sample times). However, if there are any significant deviations from nominal sample times, some concentration data may be excluded from mean concentration-time plots and/or additional concentration-time plots of the mean data may be provided. All deviations and excluded data will be provided and discussed in the CSR.

6.2 Bioanalytical Method

6.2.1 Acalabrutinib

Plasma concentrations of acalabrutinib will be determined using validated bioanalytical methods at Covance Laboratories, (Indianapolis, Indiana). The analytical range for acalabrutinib is expected to be 1.00 to 1000 ng/mL.

Unbound plasma concentrations of acalabrutinib may be determined by an appropriate method at Sekisui Medical, Drug Development Solutions Center, (Naka-gun, Ibaraki, Japan) for determination of protein binding.

6.2.2 ACP-5862

Plasma concentrations of ACP-5862 will be determined using validated bioanalytical methods at Covance Laboratories, (Indianapolis, Indiana). The analytical range for ACP-5862 is expected to be 5 to 5000 ng/mL.

Unbound plasma concentrations of ACP-5862 may be determined by an appropriate method at Sekisui Medical, Drug Development Solutions Center (Naka-gun, Ibaraki, Japan) for determination of protein binding.

6.3 Investigational Product and PK Analyte Information

The molecular formula and molecular weight (MW) of acalabrutinib are provided below:

- Molecular Formula: $C_{26}H_{23}N_7O_2$
- MW: 465.5 g/mol

The molecular formula and MW of ACP-5862 are provided below:

- Molecular Formula: $C_{26}H_{23}N_7O_3$
- MW: 481.5 g/mol

6.4 Pharmacokinetic Concentrations

Plasma concentrations of acalabrutinib and ACP-5862 as determined at the collection times and per the bioanalytical method described in Section 6.1 and Section 6.2, respectively, will be used for the calculation of the plasma acalabrutinib and ACP-5862 PK parameters.

6.5 Non-Compartmental Pharmacokinetic Analysis and Parameter Calculation

6.5.1 Plasma Pharmacokinetic Parameters

The appropriate noncompartmental PK parameters will be calculated from the plasma acalabrutinib and ACP-5862 (total and unbound) concentration-time data using Phoenix® WinNonlin® Version 7.0 or higher. Actual sample times will be used in the calculations of the PK parameters. The calculation of the actual time will be in respect to the dose administration time of acalabrutinib. All PK parameters included in the protocol are listed in Table 6.1 below, and are defined as appropriate for study design.

Table 6.1. Non-compartmental Plasma Pharmacokinetic Parameters to be Calculated

Parameter	Label to be Used in Post-Text Tables	Definition	Method of Determination
$AUC_{0\text{-last}}$	AUC0-last	Area under the concentration-time curve from time 0 to the time of the last observed/measured non-zero concentration.	Calculated using the Linear Trapezoidal with Linear Interpolation Method.
$AUC_{0\text{-}24}$	AUC0-24	Area under the concentration-time curve from time 0 to the 24-hour timepoint. If the 24-hour plasma concentration is missing, below the limit of quantification or not reportable, then this parameter cannot be calculated.	Calculated using the Linear Trapezoidal with Linear Interpolation Method.
$AUC_{0\text{-inf}}$	AUC0-inf	Area under the concentration-time curve from time 0 extrapolated to infinity.	$AUC_{0\text{-inf}} = AUC_{0\text{-last}} + (C_{last}/k_{el})$ where C_{last} is the last observed/measured concentration.

Parameter	Label to be Used in Post-Text Tables	Definition	Method of Determination
$AUC_{\%extrap}$	AUC%extrap	Percent of $AUC_{0\text{-}inf}$ extrapolated.	Calculated as: (1-[$AUC_{0\text{-}last}$/$AUC_{0\text{-}inf}$]) x100.
C_{max}	Cmax	The maximum observed concentration.	Taken directly from bioanalytical data.
T_{max}	Tmax	The time to reach C_{max}. If the maximum value occurs at > 1 timepoint, T_{max} is defined as the first timepoint with this value.	Taken from clinical database as the difference in the time of administration and the time of the blood draw which is associated with the C_{max}.
T_{last}	Tlast	Time of the last measurable concentration.	Taken from clinical database as the difference in the time of administration and the time of the blood draw which is associated with the last measurable concentration.
K_{el}	Kel	Apparent first-order terminal elimination rate constant calculated from a semi-log plot of the plasma concentration versus time curve.	Calculated by linear least-squares regression analysis using the maximum number of points in the terminal log-linear phase (eg, 3 or more non-zero plasma concentrations).
$t_{1/2}$	t1/2	Apparent first-order terminal elimination half-life.	Calculated as 0.693/Kel.
CL/F	CL/F	The apparent total plasma clearance after oral administration (calculated for acalabrutinib only).	Calculated as Dose/($AUC_{0\text{-}inf}$).
V_z/F	Vz/F	The apparent volume of distribution during the terminal elimination phase after oral administration (calculated for acalabrutinib only).	Calculated as Dose/($AUC_{0\text{-}inf}$ x K_{el}).
MR_C_{max}	MR_Cmax	Metabolite-to-parent molar ratio of C_{max}.	Calculated as: $C_{maxmetabolite}$ /$C_{maxparent}$ x MW_{parent} / $MW_{metabolite}$
MR_$AUC_{0\text{-}last}$	MR_AUC0-last	Metabolite-to-parent molar ratio of $AUC_{0\text{-}last}$.	Calculated as: $AUC_{metabolite}$ /AUC_{parent} x MW_{parent} / $MW_{metabolite}$
MR_$AUC_{0\text{-}inf}$	MR_AUC0-inf	Metabolite-to-parent molar ratio of $AUC_{0\text{-}inf}$.	Calculated as: $AUC_{metabolite}$ /AUC_{parent} x MW_{parent} / $MW_{metabolite}$

Parameter	Label to be Used in Post-Text Tables	Definition	Method of Determination
f_u	fu	Fraction of unbound drug in plasma (if evaluated).	Taken from bioanalytical data.

Pharmacokinetic parameters will not be calculated for subjects with ≤ 2 consecutive post-dose timepoints with quantifiable concentrations. Subjects for whom there are insufficient data to calculate the PK parameters will be included in the concentration tables only and excluded from the statistical analysis.

For the calculation of the PK parameters, plasma concentrations below the limit of quantitation (BLQ) before the first quantifiable concentration will be set to 0 and plasma concentrations BLQ after the first quantifiable concentration will be treated as missing.

The K_{el} will be determined using linear regressions composed of least 3 data points. The K_{el} will not be assigned if 1) the terminal elimination phase is not apparent, 2) if T_{max} is one of the 3 last data points, or 3) if the R^2 value is <0.75. In cases where the K_{el} interval is not assigned, the values of $t_{½}$, $AUC_{0\text{-inf}}$, CL/F, and V_z/F are considered not calculable and will not be reported. Wherever the resulting $t_{½}$ is > half as long as the sampling interval, the Kel values and associated parameters ($t_{½}$, $AUC_{0\text{-inf}}$, CL/F, and V_z/F) will be presented as judged appropriate and in accordance with Celerion SOPs, but may be flagged.

6.5.2 Urine Pharmacokinetic Parameters

The following PK parameters will be calculated from urine acalabrutinib and ACP-5862 data using SAS®.

Table 6.2. Noncompartmental Urine Pharmacokinetic Parameters to be Calculated

Parameter	Label to be Used in Post-Text Tables	Definition	Method of Determination
$Conc_{t1\text{-}t2}$	Conct1-t2	Drug concentration in the urine during the urine collection interval from t1 to t2	Taken directly from bioanalytical data
$Vol_{t1\text{-}t2}$	Volt1-t2	Sum of volume of urine collected over the entire urine collection interval from t1-t2	Taken directly from CRF data
$Ae_{t1\text{-}t2}$	Aet1-t2	Amount of drug excreted in the urine collection interval from t1 to t2	Calculated as (Conct1-t2 x Volt1-t2)

Parameter	Label to be Used in Post-Text Tables	Definition	Method of Determination
CumAe	CumAe	Cumulative amount of drug excreted in the urine following a single dose administration	Calculated as $Ae = \sum_{i=1}^{n-1} Ae_i (t_i - t_{i+1})$ where t1 = 0 and tn = t and Aei is measured between ti and ti+1, i=1,…,nth interval
%Dose	%Dose	The percent of dose excreted into urine during the urine collection interval from t1 to t2 (calculated for acalabrutinib only).	Calculated as [Aet1-t2]/Dose x 100
Cum%Dose	Cum%Dose	The percent of dose excreted into urine over the entire sampling interval (calculated for acalabrutinib only).	Calculated as [CumAe]/Dose x 100
CL_r	CLr	Renal clearance	Calculated as Aet'-t" /AUCt'-t" where t- t" is the longest interval of time during which Ae and AUC are both obtained.

For the calculation of descriptive statistics and urine PK parameters, urine concentrations that are BLQ will be set to zero. If a subject is unable to void, urine volume will be listed as 0 for the calculation of urine parameters (eg, amounts). Cumulative urine PK parameters (eg, CumAe) and derived parameters (eg, %Dose and Cum%Dose) for and after an unable to void interval will continue to be presented and included in summary statistics. Cumulative urine PK parameters and derived parameters after a missing sample (eg, lost part of void, volume not recorded, etc.) will continue to be presented, but will be excluded from the summary statistics.

6.6 Data Summarization and Presentation

All plasma and urine PK concentrations and/or PK parameters descriptive statistics will be generated using SAS®.

The plasma and urine concentrations of acalabrutinib and ACP-5862 will be tabulated by subject group (severe HI or Normal) and listed by nominal sample time for all subjects in the PK Population. All BLQ values will be presented as "BLQ" in the concentration table listings and footnoted accordingly. Plasma PK parameters of acalabrutinib and ACP-5862 will be tabulated by subject group and listed by parameter for all subjects in the PK Population.

Summary statistics, including sample size (n), arithmetic mean (Mean), standard deviation (SD), coefficient of variation (CV%), standard error of the mean (SEM), minimum, median, and maximum will be calculated for all nominal concentration

timepoints and PK parameters. In addition, geometric mean (Geom Mean), geometric CV (Geom CV%) will be calculated for PK parameters. Excluded subjects will be included in the concentration listings but will be excluded from the summary statistics and noted as such in the tables. All BLQ values will be presented as "BLQ" in the concentration listings and footnoted accordingly.

Plasma and urine concentrations of acalabrutinib and ACP-5862 will be presented with the same level of precision as received from the bioanalytical laboratory. Plasma and urine PK parameters will be reported to 3 significant figures for individual parameters, with the exception of T_{max}, T_{last}, and $t_{½}$ (2 decimal places), C_{max}, which will be presented in the same precision as the bioanalytical data, and urine volume which will be presented with the same precision as reported in the CRF.

The level of precision for each statistic will be presented as follows:

- minimum/maximum with the same precision as in individual data
- Arithmetic mean, median and geometric mean with one more level of precision than minimum/maximum
- SD with one more level of precision than mean/median
- n will be presented as an integer
- CV% will be presented to 1 decimal place.

Mean and individual concentration-time profiles will be presented on linear and semi-log scales. Linear mean plots will be presented with and without SD.

The relationship between acalabrutinib and ACP-5862 PK and HI will be visually assessed via scatter plots of acalabrutinib and ACP-5862 PK parameters versus the Child-Pugh score, including the data from severe HI subjects and normal hepatic function subjects as reference.

Relationships between acalabrutinib and ACP-5862 PK parameters and Child-Pugh scores, bilirubin and albumin levels, and prothrombin time will be assessed graphically.

6.7 Statistical Analysis of PK Parameters

Individual $AUC_{0\text{-inf}}$, $AUC_{0\text{-last}}$, $AUC_{0\text{-24}}$, and C_{max} values of total and unbound acalabrutinib and ACP-5862 after a single dose administration of 50 mg acalabrutinib to subjects with severe HI and matched control subjects (matched by age, weight, and sex to subjects with severe HI) will be ln-transformed and evaluated with an analysis of variance (ANOVA) model using PROC MIXED of SAS®. The ANOVA model will include subject group as a fixed effect. The inferential results (least-squares means [LSM], difference between LSMs, and 90% CIs of the difference) will be exponentiated to the original scale. Geometric LSMs, geometric mean ratios (GMR) and 90% CIs will be presented.

The ANOVA analysis will be performed using the following SAS® code:

```
PROC MIXED;
CLASS GROUP SUBJECT;
MODEL PK_PARAMETER=GROUP / ddfm=kr;
REPEATED/GROUP = GROUP;
LSMEANS GROUP/e diff cl alpha = 0.1
ESTIMATE "Severe HI vs. Normal" GROUP 1 -1/ cl alpha=0.1 e;
ODS output Estimates = LS_Diffs LSMeans = LS_Means CovParms = MSE ;
```

where GROUP is C for Severe HI and N for Normal.

7. SAFETY

All case report form (CRF) data will be listed by subject and chronologically by assessment timepoints. This will include rechecks, unscheduled assessments, and early termination.

Applicable continuous variables will be summarized using n, arithmetic mean, SD, minimum, median, and maximum.

The level of precision will be presented as follows: minimum/maximum in the same precision as in the database, mean/median in one more precision level than minimum/maximum, SD in one more precision level than mean/median, and n will be presented as an integer.

Where individual data points are missing because of dropouts or other reasons, the data will be summarized based on reduced denominators.

7.1 Subject Discontinuation

Subjects will be summarized by number of subjects dosed, completed, and discontinued the study with discontinuation reasons by group (Severe HI and Normal) and overall.

7.2 Demographics

Descriptive statistics will be calculated for continuous variables (age, weight, height, and body mass index) by group and overall.

Frequency counts will be provided for categorical variables (race, ethnicity, and sex) for each group and overall.

7.3 Adverse Events

All adverse events (AEs) occurring during this clinical study will be coded using the Medical Dictionary for Regulatory Activities (MedDRA®), Version 21.1.

All AEs captured in the database will be listed in by-subject data listings including verbatim term, coded term, treatment, severity, relationship to study medication, and action; however, only treatment-emergent AEs (TEAEs) will be summarized.

A TEAE is defined as an AE that is starting or worsening at the time of or after study drug administration. Each TEAE will be attributed to treatment based on the onset date and time of the AE.

If the onset time of an AE is missing and the onset date is the same as the treatment dosing date, then the AE will be considered treatment emergent. If onset time of an AE is missing and the onset date does not fall on a dosing date, then the AE will be considered treatment emergent. If the onset date of an AE is missing, then the AE will be considered treatment emergent unless the onset date is known to have occurred before treatment dosing.

TEAEs will be tabulated by System Organ Class (SOC) and Preferred Term. Summary tables will include number of subjects reporting the AE and as percent of number of subjects dosed by group and overall. The number of AEs will be tabulated in a similar manner. Tables which tabulate the number of TEAEs by severity and relationship to study treatment will also be included.

Serious adverse events (SAEs), if present, will also be listed. Applicable narratives will be included in the CSR.

AE of special interest (AESI) are any AEs related to risk of serous bleeding as follow and will be discussed in the CSR:

- Symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intra-articular or pericardial, or intramuscular with compartment syndrome
- Bleeding causing a fall in hemoglobin level of ≥ 20 g/L or leading to transfusion of ≥ 2 units of whole blood or red cells
- Bleeding resulting in a serious adverse drug experience (as defined in Section 13.2.5.2 of the protocol)

7.4 Clinical Laboratory Tests (Serum Chemistry, Hematology, Urinalysis)

Serum chemistry, hematology and urinalysis will be performed at Screening, Check-in, 24 hours (Day 2) postdose and for severe HI subjects only 72 hours (Day 4) postdose.

Out-of-range and clinically significant lab values will be listed.

For all numeric laboratory values, descriptive statistics will be presented for each laboratory test by assessment timepoint and group. Change from baseline will be summarized in a similar manner. Baseline is defined as the result closest to and before the dose which may include unscheduled or recheck results. This will typically

be the result collected on Check-in (Day -1). Postdose unscheduled events or early termination results will not be included in summaries.

For each laboratory test, a shift table will be developed to compare the frequency of the results at baseline (above normal, normal, or below normal) with the respective postdose results. For urinalysis tests, the categories are normal and outside normal.

7.5 Vital Signs

Vital signs (heart rate, blood pressure, respiratory rate and temperature) will be assessed at Screening, predose and for normal subjects 24 hours (Day 2) and severe HI subjects 72 hours (Day 4) postdose.

Descriptive statistics will be presented for each vital sign parameter by assessment timepoint and group. Change from baseline will be summarized in a similar manner. Baseline is defined as the result closest to and before the dose which may include unscheduled recheck results. This will typically be the result collected at predose on Day 1 (within 24 hours before dosing). Postdose unscheduled events or early termination results will not be included in summaries.

7.6 Electrocardiogram

12-lead safety ECG (heart rate, blood pressure, respiratory rate and temperature) will be assessed at Screening, predose and for normal subjects 24 hours (Day 2) and severe HI subjects 72 hours (Day 4) postdose.

Descriptive statistics will be presented for each vital sign parameter by assessment timepoint and group. Change from baseline will be summarized in a similar manner. Baseline is defined as the result closest to and before the dose which may include unscheduled recheck results. This will typically be the result collected at predose on Day 1 (within 24 hours before dosing). Postdose unscheduled events or early termination results will not be included in summaries.

ECG results will be listed for each subject with QTcF >450 msec or QTcF increase from baseline >30 msec will be flagged.

7.7 Concomitant Medications

All concomitant medications recorded during the study will be coded with the WHO Dictionary Version SEP2018 B3 and listed.

7.8 Physical Examination

Physical examinations will be performed at Screening, Check-in and for normal subjects 24 hours (Day 2) and severe HI subjects 72 hours (Day 4) postdose. Abnormal findings will be reported as medical history or adverse events. All data found in the CRF will be listed.

8. SUMMARY OF CHANGES FROM PROTOCOL-PLANNED ANALYSIS

The analyses described in this SAP are aligned with those analyses described in the protocol.

9. SUMMARY TABLES AND FIGURES

Summary tables and figures are numbered following the International Conference on Harmonization (ICH) structure but may be renumbered as appropriate during the compilation of the tables and figures for the CSR. Note that all PK and Safety summary tables and figures will be generated using SAS® Version 9.3 or higher.

9.1 In-text Summary Tables and Figures

The following is a list of table and figure titles that will be included in the text of the CSR. Tables and figures will be numbered appropriately during compilation of the CSR.

Section 10:

Table 10-1 Disposition Summary

Section 11:

Table 11-1 Demographic Summary

Table 11-2 Summary of Total Plasma Acalabrutinib Pharmacokinetic Parameters

Table 11-3 Summary of Statistical Comparisons of Total Plasma Acalabrutinib Pharmacokinetic Parameters – Group C versus Group N

Table 11-4 Summary of Unbound Plasma Acalabrutinib Pharmacokinetic Parameters

Table 11-5 Summary of Statistical Comparisons of Unbound Plasma Acalabrutinib Pharmacokinetic Parameters – Group C versus Group N

Table 11-6 Summary of Total Plasma ACP-5862 Pharmacokinetic Parameters

Table 11-7 Summary of Total Statistical Comparisons of Plasma ACP-5862 Pharmacokinetic Parameters – Group C versus Group N

Table 11-8 Summary of Unbound Plasma ACP-5862 Pharmacokinetic Parameters

Table 11-9 Summary of Statistical Comparisons of Unbound Plasma ACP-5862 Pharmacokinetic Parameters – Group C versus Group N

9.2 Section 14 Summary Tables and Figures

The following is a list of table and figure titles that will be included in Section 14 of the report. Table and figure titles may be renumbered as appropriate during the compilation of the report.

14.1 Demographic Data Summary Tables

Table 14.1.1 Summary of Disposition (Safety Population)
Table 14.1.2 Summary of Demographics (Safety Population)

14.2 Pharmacokinetic Data Summary Tables and Figures

14.2.1 Acalabrutinib Tables and Figures

14.2.1.1 Total Plasma Acalabrutinib Tables

Table 14.2.1.1.1 Total Plasma Acalabrutinib Concentrations (ng/mL) Following a Single Oral Dose of 50 mg acalabrutinib in Subjects With Severe Hepatic Impairment (Child-Pugh C) (Pharmacokinetic Population)
Table 14.2.1.1.2 Total Plasma Acalabrutinib Concentrations (ng/mL) Following a Single Oral Dose of 50 mg acalabrutinib in Subjects With Normal Hepatic Function (Healthy Control) (Pharmacokinetic Population)
Table 14.2.1.1.3 Total Plasma Acalabrutinib Pharmacokinetic Parameters Following a Single Oral Dose of 50 mg acalabrutinib in Subjects With Severe Hepatic Impairment (Child-Pugh C) (Pharmacokinetic Population)
Table 14.2.1.1.4 Total Plasma Acalabrutinib Pharmacokinetic Parameters Following a Single Oral Dose of 50 mg acalabrutinib in Subjects With Normal Hepatic Function (Healthy Control) (Pharmacokinetic Population)
Table 14.2.1.1.5 Intervals (Hours) Used for Determination of Total Plasma Acalabrutinib Kel Values (Pharmacokinetic Population)
Table 14.2.1.1.6 Statistical Comparisons of Total Plasma Acalabrutinib Pharmacokinetic Parameters: Severe Versus Healthy (Pharmacokinetic Population)

14.2.1.2 Total Plasma Acalabrutinib Figures

Figure 14.2.1.2.1 Mean (SD) Total Plasma Acalabrutinib Concentration Versus Time Profiles Following a Single Oral Dose of 50 mg Acalabrutinib (Linear Scale) (Pharmacokinetic Population)

14.2.1.3 Unbound Plasma Acalabrutinib Tables

14.2.1.4 Unbound Plasma Acalabrutinib Figures

14.2.1.5 Urine Acalabrutinib Tables

14.2.1.6 Urine Acalabrutinib Figures

14.2.2 ACP-5862 Tables and Figures

14.2.2.1 Total Plasma ACP-5862 Tables

14.2.2.2 Total Plasma ACP-5862 Figures

14.2.2.3 Unbound Plasma ACP-5862 Tables

14.2.2.4 Unbound Plasma ACP-5862 Figures

14.2.2.5 Urine ACP-5862 Tables

14.2.2.6 Urine ACP-5862 Figures

14.3 Safety Data Summary Tables

14.3.1 Displays of Adverse Events

Table 14.3.1.1 Treatment-emergent Adverse Event Frequency by Group – Number of Subjects Reporting the Event (% of Subject Dosed) (Safety Population)

Table 14.3.1.2 Treatment-emergent Adverse Event Frequency by Group – Number of Adverse Events (% of Total Adverse Events) (Safety Population)

Table 14.3.1.3 Treatment-emergent Adverse Event Frequency by Group, Severity, and Relationship to Drug – Number of Adverse Events (Safety Population)

14.3.2 Listings of Deaths, other Serious and Significant Adverse Events

Table 14.3.2.1 Serious Adverse Events (Safety Population)

<if no serious adverse event occurred, a statement 'No serious adverse event is reported'>

14.3.3 Narratives of Deaths, other Serious and Certain other Significant Adverse Events

14.3.4 Abnormal Laboratory Value Listing (each patient)

Table 14.3.4.1 Out-of-Range Values and Recheck Results – Serum Chemistry (Safety Population)

Table 14.3.4.2 Out-of-Range Values and Recheck Results – Hematology (Safety Population)

Table 14.3.4.3 Out-of-Range Values and Recheck Results – Urinalysis (Safety Population)

14.3.5 Displays of Other Laboratory, Vital Signs, Electrocardiogram, Physical Examination, and Other Safety Data

Table 14.3.5.1 Clinical Laboratory Summary and Change from Baseline – Serum Chemistry (Safety Population)

Table 14.3.5.2 Clinical Laboratory Shift from Baseline – Serum Chemistry (Safety Population)

Table 14.3.5.3 Clinical Laboratory Summary and Change from Baseline – Hematology (Safety Population)

Table 14.3.5.4 Clinical Laboratory Shift from Baseline – Hematology (Safety Population)

Table 14.3.5.5 Clinical Laboratory Summary and Change from Baseline – Urinalysis (Safety Population)

Table 14.3.5.6	Clinical Laboratory Shift from Baseline – Urinalysis (Safety Population)
Table 14.3.5.7	Vital Sign Summary and Change from Baseline (Safety Population)
Table 14.3.5.8	12-Lead Electrocardiogram Summary and Change from Baseline (Safety Population)

9.3 Section 16 Data Listings

Data listings are numbered following the ICH structure but may be renumbered as appropriate during the compilation of the TFLs for the CSR. The following is a list of appendix numbers and titles that will be included as data listings:

16.1 Study Information

Appendix 16.1.9	Statistical Methods
Appendix 16.1.10.1	Clinical Laboratory Reference Ranges

16.2 Subject Data Listings

16.2.1 Subject Discontinuation

Appendix 16.2.1	Disposition (Safety Population)

16.2.2 Protocol Deviations

Appendix 16.2.2	Protocol Deviations

16.2.3 Subjects Excluded from Pharmacokinetic Analysis

Appendix 16.2.3	Subjects Excluded from Pharmacokinetic Analysis

Note: Appendices 16.2.2 and 16.2.3 are generated in MS Word for inclusion in the study report.

16.2.4 Demographic Data

Appendix 16.2.4.1	Demographics (Safety Population)
Appendix 16.2.4.2	Child-Pugh Classification (Safety Population)
Appendix 16.2.4.3	Creatinine Clearance (Safety Population)
Appendix 16.2.4.4.1	Physical Examination -Traditional Approach (Safety Population)
Appendix 16.2.4.4.2	Physical Examination -Symptom Driven (Safety Population)

Appendix 16.2.4.5 Medical and Surgical History (Safety Population)
Appendix 16.2.4.6 Alcohol Screen (Safety Population)
Appendix 16.2.4.7 Tobacco Use (Safety Population)

16.2.5 Compliance and/or Drug Concentration Data

Appendix 16.2.5.1 Subject Eligibility (Safety Population)
Appendix 16.2.5.2 Acalabrutinib Administration (Safety Population)
Appendix 16.2.5.3 Blood Collection - Acalabrutinib and ACP-5862 PK (Safety Population)
Appendix 16.2.5.4 Blood Collection – Protein Binding (Safety Population)
Appendix 16.2.5.5 Urine Collection – Acalabrutinib and ACP-5862 PK (Safety Population)
Appendix 16.2.5.6 Prior and Concomitant Medications (Safety Population)

16.2.6 Individual Pharmacokinetic Response Data

Appendix 16.2.6.1 Plasma Acalabrutinib (Unbound and Total) Concentrations Versus Time (Linear and Semi-Log Scale) for Subject #
Appendix 16.2.6.2 Plasma ACP-5862 (Unbound and Total) Concentrations Versus Time (Linear and Semi-Log Scale) for Subject #
Appendix 16.2.6.3 Protein Binding Parameters

Programmer's note: graphs for each subject will have 2 profiles: 1 for unbound concentrations and 1 for total concentrations.

16.2.7 Adverse Events Listings

Appendix 16.2.7.1.1 Adverse Events (I of II) (Safety Population)
Appendix 16.2.7.1.2 Adverse Events (II of II) (Safety Population)
Appendix 16.2.7.2 Adverse Event Preferred Term Classification (Safety Population)

16.2.8 Listings of Individual Laboratory Measurements and Other Safety Observations

Appendix 16.2.8.1.1 Clinical Laboratory Report - Serum Chemistry (Safety Population)
Appendix 16.2.8.1.2 Clinical Laboratory Report - Hematology (Safety Population)
Appendix 16.2.8.1.3 Clinical Laboratory Report - Urinalysis (Safety Population)
Appendix 16.2.8.1.4 Clinical Laboratory Report - Urine Drug Screening (Safety Population)

10. TABLE AND FIGURE SHELLS

The following table shells provide a framework for the display of data from this study. The shells may change due to unforeseen circumstances. These shells may not be reflective of every aspect of this study, but are intended to show the general layout of the tables that will be presented and included in the final report. Unless otherwise noted, all tables will be presented in Times New Roman font size 8. These tables will be generated off of the Celerion ADaM Version 2.1data structure.

11. LISTING SHELLS

The following listing shells provide a framework for the display of data from this study. The shells may change due to unforeseen circumstances. These shells may not be reflective of every aspect of this study, but are intended to show the general layout of the listings that will be presented and included in the final report. These listings will be generated off of the Celerion SDTM Tabulation Model 1.4 mapped in accordance with SDTM Implementation Guide 3.2. All listings will be presented in Courier New size font 9.