Protocol C1061013

A PHASE 1, NON-RANDOMIZED, OPEN-LABEL, SINGLE-DOSE, PARALLEL COHORT STUDY TO COMPARE THE PHARMACOKINETICS OF PF-06835919 IN ADULT PARTICIPANTS WITH VARYING DEGREES OF HEPATIC IMPAIRMENT RELATIVE TO PARTICIPANTS WITHOUT HEPATIC IMPAIRMENT

Statistical Analysis Plan
(SAP)

Version: **2**

Date: **03-SEP-2021**

NOTE: Italicized text within this document has been taken verbatim from the Protocol.

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1. VERSION HISTORY

Table 1. Summary of Changes

Version/ Date	Associated Protocol Amendment	Rationale	Specific Changes
1 13 Nov 2019	Original 23 Sep 2019	N/A	N/A
2 03 SEP 2021	Amendment 1 18 Feb 2021 PACL 1 30 Oct 2019 PACL 2 10 Mar 2020 PACL 3 20 Oct 2020 PACL 4 04 Nov 2020 PACL 5 14 Dec 2020	Amendment, PACLs and BDR	• Version 1 transferred to new SAP template (some sections have been moved and edited to accommodate new template; some additional text also added) • Section 4: Duplicate/redundant text removed • Section 6.2.5: Correction to baseline definition for lab data • Section 6.2.6: Additional text added for clarification of baseline definition for vitals • Appendix 1: Added 'gender' into CLASS statement • Appendix 2: Added text for summary of the number of participants with uncorrected QT values >500 msec; corrected units for ECG endpoints

2. INTRODUCTION

The primary purpose of this non-randomized, single dose, open-label study is to characterize the effect of varying degrees of hepatic impairment on the plasma pharmacokinetics (PK) of PF-06835919 following administration of a single, oral, 25 mg dose. NAFLD/NASH is associated with varying degrees of hepatic impairment. Recognizing that the target population of PF-06835919 is patients with NAFLD/NASH and that the major clearance mechanism of PF-06835919 is predicted to be active uptake into the liver followed by metabolism in the liver, the current study is proposed to evaluate whether there is any clinically meaningful effect of hepatic impairment on the plasma PK of PF-06835919.

This statistical analysis plan (SAP) provides the detailed methodology for summary and statistical analyses of the data collected in Study C1061013. This document may modify the plans outlined in the protocol; however, any major modifications of the primary endpoint definition or its analysis will also be reflected in a protocol amendment.

2.1. Study Objectives, Endpoints, and Estimands

Objectives	*Endpoints*
Primary:	***Primary:***
• *To compare the PK of PF-06835919 (both total and unbound) following administration of a single oral dose in adult participants with varying degrees of hepatic impairment relative to age- and body weight-matched participants without hepatic impairment.*	• *PF-06835919 PK parameters derived from plasma: C_{max}, AUC_{inf}, f_u, $C_{max,u}$, and $AUC_{inf,u}$.*
Secondary:	***Secondary:***
• *To evaluate the safety and tolerability of a single oral dose of PF-06835919 when administered to adult participants with varying degrees of hepatic impairment relative to age- and body weight-matched participants without hepatic impairment.*	• *Assessment of treatment-emergent adverse events, clinical laboratory tests, vital signs, and 12-lead ECGs.*
CCI [redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

There are no estimands for this study.

2.2. Study Design

This is a non-randomized, open label, single dose, parallel cohort, multicenter study to investigate the effect of varying degrees of hepatic function on the plasma PK (total and unbound) of PF-06835919 after a single oral 25 mg dose administered in the fed state. A total of approximately 24 participants with varying degrees of hepatic function will be enrolled into the study to ensure that approximately 6 evaluable participants in each of the 3 hepatic impairment cohorts, and 6 to 8 in the cohort without hepatic impairment complete the study. Participants will be selected based on their Child Pugh score as shown in Table 2.

Table 2. Hepatic Function Categories Based on Child Pugh Score

Cohort	Description	Child-Pugh Score	Number of Subjects
1	Without hepatic impairment	Not Applicable	6-8[a]
2	Mild hepatic impairment	Class A (5 to 6 points)	6
3	Moderate hepatic impairment	Class B (7 to 9 points)	6
4	Severe hepatic impairment	Class C (10 to 15 points)	4-6[b]

a. Additional participants may be dosed to a maximum of 8 participants to ensure mean age ±5 years and mean body weight ±10 kg of this cohort is aligned with the pooled average assessed when 75% of participants are dosed across the 3 hepatic impairment cohorts.

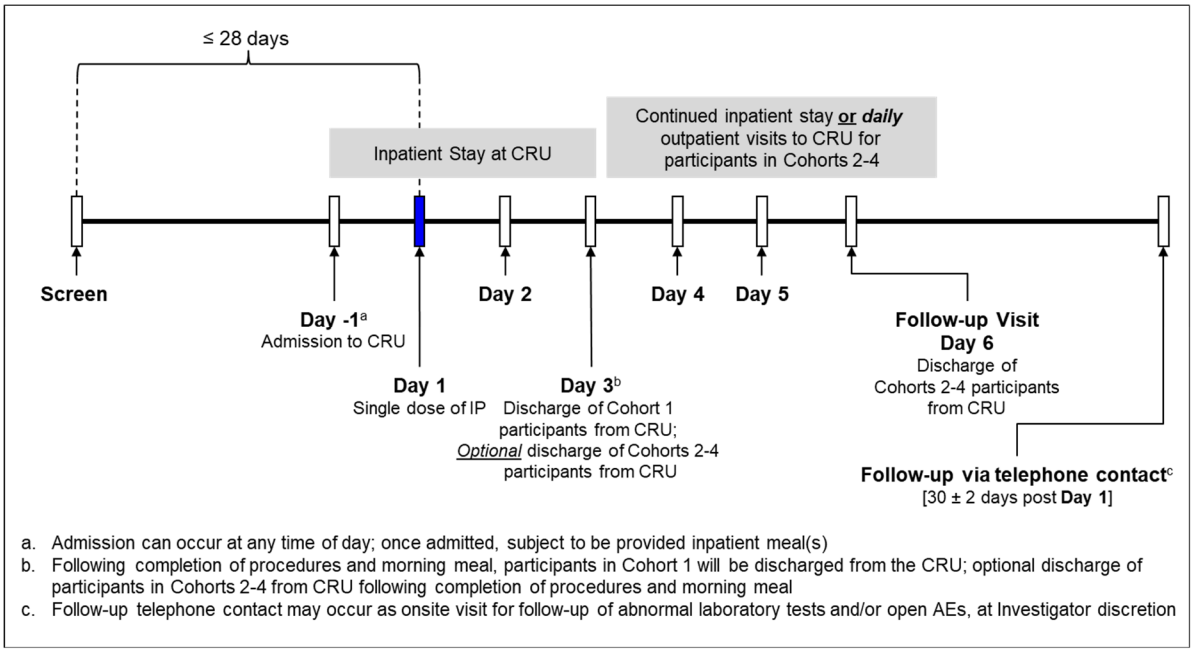
b. If recruitment across the sites selected proves to be prohibitive, study will dose only 4 participants in this cohort.

Child-Pugh scores will be determined at the screening visit. Participants will be enrolled in a staged manner such that participants with moderate and severe hepatic impairment (Cohorts 3 and 4) will be evaluated first. Enrollment of participants with mild hepatic impairment (Cohort 2) will occur when approximately 50% of the total participants in Cohorts 3 and 4 have been enrolled. Participants without hepatic impairment (Cohort 1) will then be enrolled near the end of the study. These participants will be recruited to match the average demographics (at a minimum, age and weight; and gender as much as practically possible) across the pooled Cohorts 2 through 4. ***Approval from the Sponsor must be obtained before proceeding with dosing participants in Cohort 1 or Cohort 2.***

Participants who prematurely discontinue for non-safety related reasons may be replaced, at the discretion of the principal investigator (PI) and Sponsor study team.

The overall study design is summarized in Figure 1. For individual participants, the total duration of participation from the Screening visit to the final clinic visit (Day 6) will be a maximum of approximately 5 weeks.

Figure 1. Study Design



a. Admission can occur at any time of day; once admitted, subject to be provided inpatient meal(s)
b. Following completion of procedures and morning meal, participants in Cohort 1 will be discharged from the CRU; optional discharge of participants in Cohorts 2-4 from CRU following completion of procedures and morning meal
c. Follow-up telephone contact may occur as onsite visit for follow-up of abnormal laboratory tests and/or open AEs, at Investigator discretion

3. ENDPOINTS AND BASELINE VARIABLES: DEFINITIONS AND CONVENTIONS

3.1. Primary Endpoint(s)

Blood samples for PK analysis of PF-06835919 will be taken according to the Schedule of Activities given in the protocol.

The following PK parameters will be calculated for PF-06835919 (if possible) from the concentration-time data using standard noncompartmental methods:

Table 3. Noncompartmental PK Parameters

PK Parameter	Analysis Scale	PF-06835919	Definition
AUC_{inf}*	ln	A, D	Area under the plasma concentration-time profile from time zero extrapolated to infinite time
$AUC_{inf,u}$*	ln	A, D	Unbound area under the plasma concentration-time curve from time zero extrapolated to infinite time
C_{max}	ln	A, D	Maximum plasma concentration
$C_{max,u}$	ln	A, D	Unbound maximum plasma concentration
f_u	R	D	Fraction unbound

Key: A=analyzed using statistical model, D=displayed with descriptive statistics, ln=natural-log transformed, R=raw (untransformed), *=if data permits

3.2. Secondary Endpoint(s)

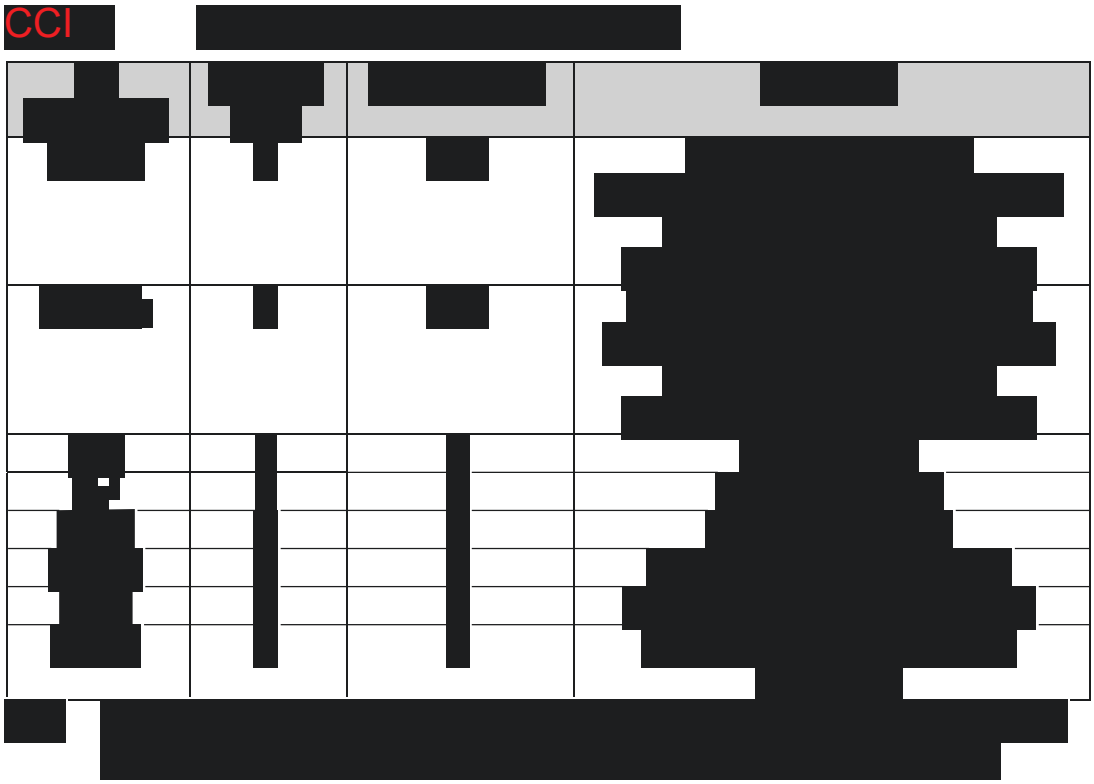
The following data are considered in standard safety summaries (see protocol for collection days and list of parameters):

- *adverse events,*
- *laboratory data,*
- *vital signs data,*
- *ECG results.*

An adverse event is considered a Treatment-Emergent Adverse Event (TEAE) if the event started during the effective duration of treatment. All events that start on or after the first dosing day and time/start time, if collected, but before the last dose plus the lag time will be flagged as TEAEs. The algorithm will not consider any events that started prior to the first dose date.

CCI [redacted]

CCI [redacted]



3.4. Baseline Variables

No covariate will be included in the model for the primary analysis (i.e. ANOVA).
As a sensitivity analysis age and body weight will be included in the model (i.e. ANCOVA).
Additionally, gender may also be included as a covariate.

3.5. Safety Endpoints

See section 3.2.

4. ANALYSIS SETS (POPULATIONS FOR ANALYSIS)

The PK concentration population will be defined as all participants *who received 1 dose of PF-06835919 and in whom at least 1 plasma concentration value is reported.*

The PK parameter analysis population is defined as all participants *dosed who have at least 1 of the PK parameters of primary interest.*

The safety analysis set will be defined as a*ll participants assigned to investigational product and who take at least 1 dose of investigational product.*

All analyses will be performed on an "as-treated" basis and will not include data from participants who are not treated.

Participants who experience events that may affect their PK profile (e.g. lack of compliance with dosing) may be excluded from the PK analysis. At the discretion of the pharmacokineticist, a concentration value may also be excluded if the deviation in sampling time is of sufficient concern or if the concentration is anomalous for any other reason.

A full list of protocol deviations for the study report will be compiled prior to database closure; only important protocol deviations will be reported in the Clinical Study Report (CSR). Any significant deviation from the protocol will be reviewed prior to database closure and a decision taken regarding evaluation for each analysis population.

5. GENERAL METHODOLOGY AND CONVENTIONS

5.1. Hypotheses and Decision Rules

There is no statistical hypothesis testing planned for this study.

No statistical decision rules are applied.

5.2. General Methods

For all outputs produced, the following ordering will be used:

1. Without Hepatic Impairment
2. Mild Hepatic Impairment
3. Moderate Hepatic Impairment
4. Severe Hepatic Impairment.

The effect of the hepatic impairment on PK parameters will be assessed by constructing 90% confidence intervals around the estimated difference between each of the Test (impaired) cohorts and the Reference (without hepatic impairment) cohort using a one-way ANOVA model based on natural log transformed data.

The relationship between PK parameters and hepatic function (eg, serum albumin concentration or prothrombin time) will be determined by a linear regression model.

5.3. Methods to Manage Missing Data

The handling of missing values for PK data is described in this section. For the analysis of safety endpoints, the sponsor data standard rules for imputation will be applied.

5.3.1. Concentrations Below the Limit of Quantification

In all data presentations (except listings), concentrations below the limit of quantification (BLQ) will be set to zero. (In listings BLQ values will be reported as "<LLQ", where LLQ will be replaced with the value for the lower limit of quantification.)

5.3.2. Deviations, Missing Concentrations and Anomalous Values

In summary tables and plots of median profiles, statistics will be calculated having set concentrations to missing if 1 of the following cases is true:

1. A concentration has been collected as ND (ie not done) or NS (ie no sample),
2. A deviation in sampling time is of sufficient concern or a concentration has been flagged anomalous by the pharmacokineticist.

Note that summary statistics will not be presented at a particular time point if more than 50% of the data are missing.

5.3.3. Pharmacokinetic Parameters

Actual PK sampling times will be used in the derivation of PK parameters.

If a PK parameter cannot be derived from a participant's concentration data, the parameter will be coded as NC (ie not calculated). (Note that NC values will not be generated beyond the day that a participant discontinues.)

In summary tables, statistics will be calculated by setting NC values to missing; and statistics will be presented for a particular hepatic function group with ≥3 evaluable measurements. For statistical analyses (ie analysis of variance), PK parameters coded as NC will also be set to missing; and analyses will not be performed for a particular parameter if more than 50% of the data are NC.

If an individual participant has a known biased estimate of a PK parameter (due for example to an unexpected event such as vomiting before all the compound is adequately absorbed in the body), this will be footnoted in summary tables and will not be included in the calculation of summary statistics or statistical analyses.

6. ANALYSES AND SUMMARIES

6.1. Primary Endpoint(s)

The following PK parameters (including both primary and tertiary endpoints) will be summarized by hepatic function group:

Table 5. PK Parameters to be Summarized Descriptively by Group

Parameter	Summary Statistics
CCI [redacted] AUC_{inf}, $AUC_{inf,u}$, C_{max}, $C_{max,u}$, CCI [redacted] CCI [redacted] and f_u	N, arithmetic mean, median, cv%, standard deviation, minimum, maximum, geometric mean and geometric cv%.
CCI [redacted]	[redacted]

Box and whisker plots for individual subject parameters (AUC_{inf}, $AUC_{inf,u}$, CCI [redacted] C_{max} and $C_{max,u}$) be presented by hepatic function group and overlaid with geometric means.

CCI [redacted]

Presentations for PF-06835919 concentrations will include:

- a listing of all concentrations sorted by hepatic function group (present in heading), subject id and nominal time post-dose. The concentration listing will also include the actual times. Deviations from the nominal time will be given in a separate listing.
- a summary of concentrations by hepatic function group and nominal time post-dose, where the set of statistics will include n, mean, median, standard deviation, coefficient of variation (cv), minimum, maximum and the number of concentrations above the lower limit of quantification.
- median concentrations time plots (on both linear and semi-log scales) against nominal time post-dose by hepatic function group (all hepatic function groups on the same plot per scale, based on the summary of concentrations by hepatic function group and time post-dose).
- mean concentrations time plots (on both linear and semi-log scales) against nominal time post-dose by hepatic function group (all hepatic function groups on the same plot per

scale, based on the summary of concentrations by hepatic function group and time post-dose).
– individual concentration time plots by hepatic function group (on both linear and semi-log scales) against actual time post-dose (there will be separate spaghetti plots for each hepatic function group per scale).

For summary statistics, median and mean plots by sampling time, the nominal PK sampling time will be used, for individual subject plots by time, the actual PK sampling time will be used.

A one-way analysis of variance (ANOVA) will be used to compare the natural log transformed PF-06835919 AUC_{inf}, CCI *C_{max}, unbound AUC_{inf} ($AUC_{inf,u}$),* CCI *and unbound C_{max} ($C_{max,u}$), as data permit, for each of the hepatic impairment cohorts (Test) to the cohort without hepatic impairment (Reference). Estimates of the adjusted mean differences (Test - Reference), and corresponding 90% confidence intervals, will be obtained from the model. These will be exponentiated to provide estimates of the ratio of adjusted geometric means (Test/Reference) and 90% confidence intervals for the ratios.*

Additionally, as a sensitivity *analysis, age,* gender *and body weight will be explored as an additional covariate/factor in the model, as appropriate.*

Linear regression will *be used to analyse the potential relationship between appropriate* natural log transformed *PK parameters [*AUC_{inf}, $AUC_{inf,u}$, CCI *] and hepatic function [serum albumin concentration, prothrombin time and* total bilirubin*]. Plots of PK parameters (eg,* AUC_{inf}, $AUC_{inf,u}$, CCI *) versus hepatic function will be constructed, with a regression line and 90% confidence region included. Estimates of the slope and intercept, together with a 90% confidence interval (CI), and the coefficient of determination* (i.e. R-squared and adj-R-squared) *will be obtained from the model.*

Residuals from the models will be examined for normality and the presence of outliers via visual inspection of plots of residuals vs predicted values and normal probability plots of residuals but these will not be included in the clinical study report. If there are major deviations from normality or outliers then the effect of these on the conclusions will be investigated through alternative transformations and/or analyses excluding outliers.

Justification for any alternative to the planned analysis will be given in the report of the study.

6.2. Secondary Endpoint(s)

A set of summary tables split by hepatic function group will be produced to evaluate any potential risk associated with the safety and toleration of administering PF-06835919.

6.2.1. Treatment and Disposition of Subjects

Participant evaluation groups will show subject disposition. Frequency counts will be supplied for participants discontinuation(s) by hepatic function group.

Data will be reported in accordance with the sponsor reporting standards.

6.2.2. Demographic and Clinical Examination Data

A summary of demographic data will be provided for age, race, weight, body mass index, and height. Each will be summarized by hepatic function group and 'Total' in accordance with the sponsor reporting standards.

6.2.3. Discontinuation(s)

Participant discontinuations will be detailed and summarized by hepatic function group.

Data will be reported in accordance with the sponsor reporting standards.

6.2.4. Adverse Events

Adverse events will be reported in accordance with the sponsor reporting standards by hepatic function group.

6.2.5. Laboratory Data

Laboratory data will be listed and summarized in accordance with the sponsor reporting standards.

The baseline measurement is the last pre-dose measurement on Day 1.

6.2.6. Vital Signs Data

The baseline measurement (for blood pressure and pulse rate) is the last pre-dose measurement on Day 1.

Absolute values and changes from baseline in seated systolic and diastolic blood pressure, and pulse rate will be summarized by hepatic function group and visit using sponsor reporting standards.

Maximum absolute values and changes from baseline for seated vital signs will be summarized descriptively by hepatic function group using categories as defined in **Appendix 2.** Numbers and percentages of participants meeting the categorical criteria will be provided. All planned and unplanned post-dose time-points will be counted in these categorical summaries. All values meeting the criteria of potential clinical concern will be listed.

These data will be listed in accordance with the sponsor reporting standards.

6.2.7. ECG Data

The baseline measurement is the last pre-dose measurement on Day 1.

Absolute and changes from baseline for the ECG parameters QT interval, heart rate, QTcF interval, PR interval, and QRS interval will be summarized by hepatic function group and visit using sponsor reporting standards.

ECG endpoints and changes from baseline (QTcF, PR and QRS) will also be summarized descriptively by hepatic function group using categories as defined in Appendix 2 (for QTc these correspond to the Pfizer Guidance in Section 9). Numbers and percentages of participants meeting the categorical criteria will be provided. All planned and unplanned post-dose time-points will be counted in these categorical summaries. All values meeting the criteria of potential clinical concern will be listed.

In addition, listings of participants with any single post-dose value >500 msec will also be produced for QTcF.

6.2.8. Concomitant Treatments

All concomitant medication(s) as well as non-drug treatment(s) will be provided in the listings.

6.3. Subset Analyses

Not applicable.

6.4. Baseline and Other Summaries and Analyses

Prior medication(s) and non-drug treatment(s), serum FSH concentrations, serum B-hCG for all females will be obtained at Screening. These data will only be listed.

A listing of Child-Pugh Classification by Severity of Hepatic Impairment will be produced.

Urine drug screen, urine B-hCG for women of child bearing potential and physical examination findings will be collected at baseline or prior to baseline visit. These data will not be brought in-house, and therefore will not be listed.

6.5. Safety Summaries and Analyses

See section 6.2.

7. INTERIM ANALYSES

7.1. Introduction

No formal interim analysis will be conducted for this study. As this is an open-label study, the sponsor may conduct unblinded reviews of the data during the course of the study for the purpose of safety assessment, facilitating PK modeling, and/or supporting clinical development.

7.2. Interim Analyses and Summaries

Not applicable.

8. REFERENCES

None.

9. APPENDICES

Appendix 1. SAS CODE FOR ANALYSES

```
/* Letter assignments for cohort within the estimate statement in the code below are as
      follows;
A = Normal (Reference)
B = Mild (Test)
C = Moderate (Test)
D = Severe (Test);
*/;
```

An example of the PROC GLM code is provided below:

```
proc glm data=tab.pk;
      class cohort;
      model l&var=cohort/ss3 clparm alpha=0.1;
      lsmeans cohort;
      estimate 'Mild vs Normal'          cohort -1 1 0 0;
      estimate 'Moderate vs Normal'      cohort -1 0 1 0;
      estimate 'Severe vs Normal'        cohort -1 0 0 1;
      ods output Estimates = est&var;
      ods output FitStatistics = fit&var;
      ods output ModelANOVA = tst&var;
      ods output OverallANOVA = overall&var;
run;
```

For ANCOVA: An example of the PROC GLM code is provided below:

```
proc glm data=tab.pk;
      class cohort gender;
      model l&var = cohort age gender weight / ss3 clparm alpha=0.1;
      lsmeans cohort;
      estimate 'Mild vs Normal'          cohort -1 1 0 0;
      estimate 'Moderate vs Normal'      cohort -1 0 1 0;
      estimate 'Severe vs Normal'        cohort -1 0 0 1;
      ods output Estimates = est&var;
      ods output FitStatistics = fit&var;
      ods output ModelANOVA = tst&var;
      ods output OverallANOVA = overall&var;
run;
```

An example of the PROC REG code is provided below:

```
proc reg data=tab.pk;
        model l&var=&HepaticFunction/clb alpha=0.1;
        ods output ParameterEstimates = param&var;
        ods output FitStatistics = fit&var;
        ods output ANOVA = reg&var;
run;
```

Appendix 2. Categorical Classes for ECG and Vital Signs of Potential Clinical Concern

Categories for QTcF

QTcF (msec)	>450 and ≤480	>480 and ≤500	>500
QTcF (msec) increase from baseline	>30 and ≤60	>60	

Categories for PR and QRS

PR (msec)	max. ≥300	
PR (msec) increase from baseline	Baseline >200 and max. ≥25% increase	Baseline ≤200 and max. ≥50% increase
QRS (msec)	max. ≥140	
QRS (msec) increase from baseline	≥50% increase	

In addition, the number of participants with uncorrected QT values >500 msec will be summarized.

Categories for Vital Signs

Systolic BP (mm Hg)	min. <90	
Systolic BP (mm Hg) change from baseline	max. decrease ≥30	max. increase ≥30
Diastolic BP (mm Hg)	min. <50	
Diastolic BP (mm Hg) change from baseline	max. decrease ≥20	max. increase ≥20
Seated pulse rate (bpm)	min. <40	max. >120

Measurements that fulfill these criteria are to be listed in report.