Protocol *A7471058*

A PHASE 1, OPEN-LABEL, SINGLE-DOSE, PARALLEL-GROUP STUDY TO EVALUATE THE PLASMA PHARMACOKINETICS AND SAFETY OF DACOMITINIB IN PARTICIPANTS WITH SEVERELY IMPAIRED HEPATIC FUNCTION RELATIVE TO PARTICIPANTS WITH NORMAL HEPATIC FUNCTION

Statistical Analysis Plan (SAP)

Version: **1.0**

SAP Author: PPD **(**FSP Statistician – Sciformix Technologies Pvt. Ltd, Mumbai**)**

Date: 11-JAN-2019

[redacted]

Revision History

Version	Date	Author(s)	Summary of Changes/Comments
1.0	January 11, 2019	PPD	Not Applicable

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

TABLE OF CONTENTS

[redacted]

LIST OF TABLES

APPENDICES

1. AMENDMENTS FROM PREVIOUS VERSION(S)

None.

2. INTRODUCTION

Dacomitinib (PF-00299804) is a selective, adenosine triphosphate (ATP) competitive, irreversible, small-molecule inhibitor of the HER (ERBB) family of receptor tyrosine kinases (RTKs), including the epidermal growth factor receptor (EGFR, HER1), the HER2 receptor (ERBB2), the HER4 receptor (ERBB4), and their oncogenic variants (eg, EGFR with del exon 19 or L858R mutations). It is currently approved for the first-line treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with EGFR-activating mutations.

Insufficient data are however available regarding the use of dacomitinib in patients with severe hepatic impairment to provide dosing recommendations in this patient population.

The purpose of this study is to evaluate the effect of severe hepatic impairment on the single dose PK of dacomitinib.

2.1. Study Design

This will be a Phase 1, open-label, parallel-group study to investigate the effect of severe hepatic impairment on the plasma PK, safety and tolerability after a single oral 30 mg dose of dacomitinib under fasted conditions.

At Screening, the modified Child-Pugh classification score as outlined in Appendix 8 of the Protocol *will be utilized to assess entry criteria and to assign participants into the appropriate hepatic impairment group* (Table 1 below). *The modified Child-Pugh classification criteria will permit enrollment of participants with a history of Stage 3 or Stage 4 encephalopathy who are receiving medication(s) to prevent recurrent encephalopathy; participants with clinically active Stage 3 or 4 encephalopathy will be excluded from participation in the study. The criteria will also allow enrollment of participants with history of severe ascites who are on medication(s) to control their ascites.*

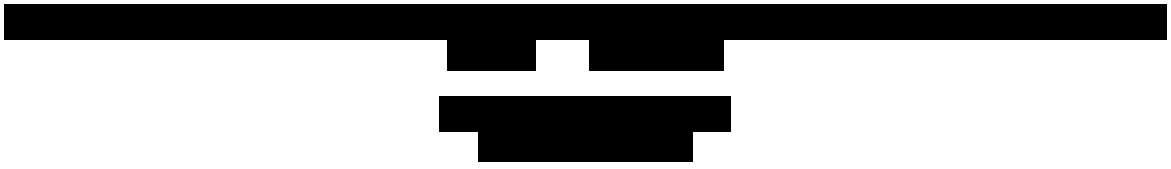


Table 1. Hepatic Function Categories Based on Child-Pugh Classification

Cohort	Description	Child-Pugh Score	Number of Participants
1	*Severe hepatic impairment*	*Class C (10 to 15 points)*	*8*
2	*Normal hepatic function*	*Not applicable*	*8*[a]

a. Participants in Cohort 2 may be dosed to a maximum of 10 participants to ensure that the age of each participant in Cohort 2 is within ±10 years and the body weight is within ±15 kg to the median age and median body weight of participants in Cohort 1, respectively.

Approximately 18 participants will be enrolled into the study to ensure at least 6 PK evaluable (having data for estimating primary PK parameters for dacomitinib) participants in each cohort. Participants who withdraw may be replaced upon agreement with the Sponsor.

*The participants from the severely impaired hepatic function cohort will be recruited first, and a median value for age and weight will be determined for all evaluable participants across study sites in this cohort. Then the control participants from the normal hepatic function cohort will be recruited later such that the age of each participant in Cohort 2 is within ±10 years and the body weight is within ±15 kg of the median of the participants in the severe hepatic impairment cohort (Cohort 1). An attempt will be made to maintain a similar male/female ratio and racial make-up between Cohorts 1 and 2. Approval from the Sponsor must be obtained **before** proceeding with dosing participants in Cohort 2.*

After the PK data from all participants with severe hepatic impairment (Cohort 1) have been reviewed, the Sponsor will notify the site if additional participants for Cohort 1 are required. If no additional participants are required, recruitment for participants with normal hepatic function (Cohort 2) will begin. If the PK variability is greater than expected, additional participants may be enrolled in Cohort 1 and the sample size for Cohort 2 will also be increased accordingly.

The end of the study is defined as the date of the last visit of the last participant in the study.

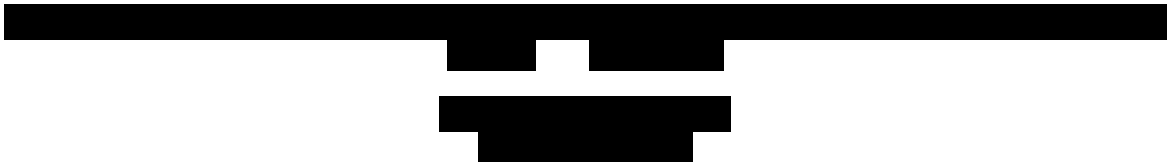
2.2. Study Objectives

Primary Objective

To evaluate the effect of severe hepatic impairment on the single dose plasma PK of dacomitinib.

Secondary Objective

To assess the safety and tolerability of a single oral dose of dacomitinib in participants with normal hepatic function and participants with severe hepatic impairment.



Tertiary/Exploratory Objectives

- *To characterize the effect of severe hepatic impairment on other plasma PK parameters of dacomitinib and its metabolite PF-05199265.*
- *To analyze CYP2D6 genotype in pharmacogenetic samples.*
- *To enable exploratory research through collection of banked biospecimens, unless prohibited by local regulations or ethics committee decision.*

3. INTERIM ANALYSES, FINAL ANALYSES AND UNBLINDING

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 dose selection decisions, and/or supporting clinical development.

Final analysis will follow the official database release. As this will be an open-label study, there is no formal unblinding of the randomization code.

4. HYPOTHESES AND DECISION RULES

4.1. Statistical Hypotheses

No hypotheses are required.

4.2. Statistical Decision Rules

No decision rules are required.

5. ANALYSIS SETS

5.1. Pharmacokinetic (PK) Analysis Set

5.1.1. Concentration Analysis Set

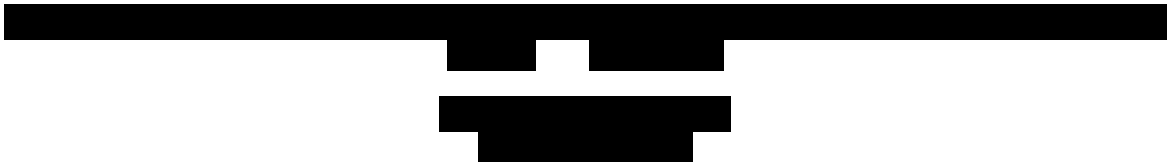
This set is defined as *all participants who take 1 dose of dacomitinib and have at least 1 dacomitinib plasma concentration.*

5.1.2. Parameter Analysis Set

This set is defined as *all participants who take 1 dose of dacomitinib and have at least 1 dacomitinib plasma PK parameters of primary interest.*

5.2. Pharmacodynamic Analysis Set

None.



5.3. Safety Analysis Set

This set is defined as *all participants assigned to dacomitinib and who take 1 dose of dacomitinib.*

5.4. Other Analysis Sets

None.

5.5. Treatment Misallocations

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

If a subject takes a treatment out of sequence or takes the same treatment twice, then they will be reported under the treatment that they actually receive for all safety, PK and pharmacodynamic analyses, where applicable.

5.6. Protocol Deviations

Subjects 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 will be compiled and reviewed to identify major and minor deviations prior to database closure.

5.6.1. Deviations Assessed Prior to Randomization

At Screening, the investigator will assess subjects against the inclusion and exclusion criteria as set out in Sections 5.1 and 5.2 of the protocol.

5.6.2. Deviations Assessed Post-Randomization

A full list of protocol deviations for the study report will be compiled prior to database closure. Any significant deviation from the protocol will be reviewed prior to database closure and a decision taken regarding evaluation for each analysis population.

6. ENDPOINTS AND COVARIATES

6.1. Efficacy Endpoint(s)

None.

6.2. Safety Endpoints

Any events occurring following start of treatment or increasing in severity will be counted as treatment emergent.

Events that occur in a non-treatment period (for example, Washout or Follow-up) will be counted as treatment emergent and attributed to the previous treatment taken.

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.*

6.3. Other Endpoints

6.3.1. PK Endpoints

Blood samples for PK analysis of dacomitinib and PF-05199265 will be taken according to the Schedule of Activities given in the protocol.

The following PK parameters will be calculated for dacomitinib and PF-05199265 (if possible) from the concentration-time data using standard noncompartmental methods:

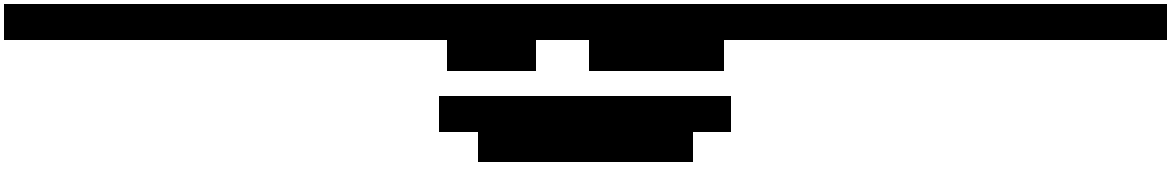


Table 2. Noncompartmental PK Parameters

PK Parameter	Analysis Scale	Dacomitinib	PF-05199265
AUC_{inf}*	ln	A, D	A, D
$AUC_{inf,u}$*	ln	A, D	A, D
AUC_{last}	ln	A, D	A, D
$AUC_{last,u}$	ln	A, D	A, D
C_{max}	ln	A, D	A, D
$C_{max,u}$	ln	A, D	A, D
T_{max}	R	D	D
$t_{1/2}$*	ln	D	D
CL/F*	ln	D	-
CL_u/F*	ln	D	-
V_Z/F*	ln	D	-
$V_{Z,u}$/F*	ln	D	-
Fu	R	D	D

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

6.3.2. PD Endpoints

None.

6.4. Covariates

None.

7. HANDLING OF MISSING VALUES

For the analysis of safety endpoints, the sponsor data standard rules for imputation will be applied.

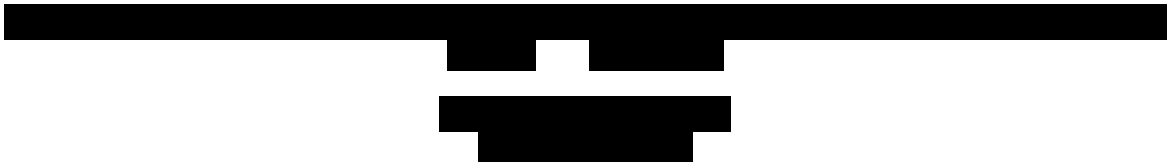
7.1. Concentrations Below the Limit of Quantification

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).

7.2. 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.

7.3. Pharmacokinetic Parameters

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

If a PK parameter cannot be derived from a subject'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 subject 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.

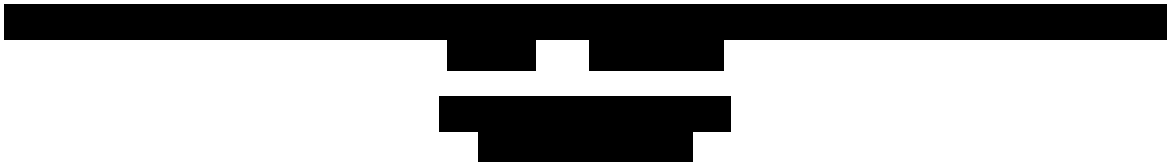
If an individual subject has a known biased estimate of a PK parameter (due for example to an unexpected event such as vomiting before all the compound is adequately absorbed in the body), this will be footnoted in summary tables and will not be included in the calculation of summary statistics or statistical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

8. STATISTICAL METHODOLOGY AND STATISTICAL ANALYSES

8.1. Statistical Methods and Analyses

The effect of hepatic impairment on PK parameters will be assessed by constructing 90% confidence intervals (CIs) around the estimated difference between the Test (severe hepatic impairment cohort; Cohort 1) and the Reference (normal hepatic function; Cohort 2) using a one-way analysis of variance (ANOVA) model based on natural log transformed data. Only participants with CYP2D6 EM and IM in each cohort will be included in this analysis.

One-way ANOVA will be used to compare the natural log transformed AUC_{inf}, AUC_{last} and C_{max}, and $AUC_{inf,u}$, $AUC_{last,u}$ and $C_{max,u}$ of dacomitinib and PF-05199265, as data permit, for severe hepatic impairment cohort (Test) to the normal hepatic function cohort (Reference). Estimates of the adjusted mean differences (Test-Reference) and corresponding 90% CIs will be obtained from the model. The adjusted mean differences and 90% CIs for the differences will be exponentiated to provide estimates of the ratio of adjusted geometric means (Test/Reference) and 90% CIs for the ratios as a percentage.



The dacomitinib PK parameters (AUC_{inf}, $AUC_{inf,u}$, AUC_{last}, $AUC_{last,u}$, C_{max}, $C_{max,u}$, T_{max}, $t_{½}$, CL/F, CL_u/F, V_z/F, and $V_{z,u}/F$) and PF-05199265 PK parameters (AUC_{inf}, $AUC_{inf,u}$, AUC_{last}, $AUC_{last,u}$, C_{max}, $C_{max,u}$, T_{max}, $t_{½}$) will be summarized descriptively by cohort. Boxplots of mean, median and individual participant parameters will be made by cohort for AUC_{inf}, $AUC_{inf,u}$, AUC_{last}, $AUC_{last,u}$, C_{max}, and $C_{max,u}$. Similar presentations will also be made for other PK parameters, if considered relevant. Dacomitinib and PF-05199265 total and unbound concentrations will be listed and summarized descriptively by PK sampling time and cohort. Summary profiles (means and medians) of the dacomitinib and PF-05199265 concentration-time data will be plotted by cohort on linear and semi-log scale. Individual participant concentration time profiles will be also presented. For summary statistics and summary plots by sampling time, the nominal PK sampling time will be used, for individual participant plots by time, the actual PK sampling time will be used.

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.

The following PK parameters will be summarized and listed by hepatic function group:

Table 3. PK Parameters to be Summarized Descriptively by Group

Parameter	Summary Statistics
AUC_{inf}, $AUC_{inf,u}$, AUC_{last}, $AUC_{last,u}$, C_{max}, $C_{max,u}$, CL/F, CL_u/F, V_z/F, and $V_{z,u}/F$	N, arithmetic mean, median, cv%, standard deviation, minimum, maximum, geometric mean and geometric cv%.
T_{max}	N, median, minimum, maximum.
$t_{1/2}$, fu	N, arithmetic mean, median, cv%, standard deviation, minimum, maximum.

Supporting data from the estimation of $t_{½}$ and AUC_{inf} will be listed by analyte and group: terminal phase rate constant (k_{el}); goodness of fit statistic from the log-linear regression (r^2); the percent of AUC_{inf} based on extrapolation ($AUC_{extrap\%}$); and the first, last, and number of time points used in the estimation of k_{el}. This data may be included in the clinical study report.

Presentations for dacomitinib and PF-05199265 concentrations will include:

- a listing of all concentrations sorted by hepatic function group (present in heading), subject id and nominal time postdose. 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 postdose, 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 postdose 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 postdose).

- mean concentrations time plots (on both linear and semi-log scales) against nominal time postdose 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 postdose).

- individual concentration time plots by hepatic function group (on both linear and semi-log scales) against actual time postdose (there will be separate spaghetti plots for each hepatic function group per scale).

- Box and whisker plots for individual subject parameters (AUC_{inf}, $AUC_{inf, u}$, AUC_{last}, $AUC_{last, u}$, C_{max}, and $C_{max, u}$) by hepatic function group and overlaid with geometric means.

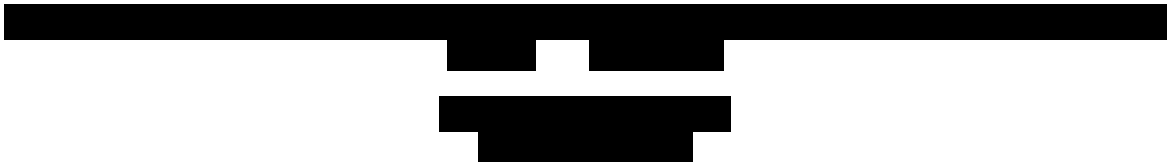
For summary statistics, median and mean plots by sampling time, the nominal PK sampling time will be used, for individual subject plots by time, the actual PK sampling time will be used.

8.2. Safety Analysis

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 study treatments.

8.2.1. Treatment and Disposition of Subjects

Subject evaluation groups will show end of study subject disposition and will show which subjects were analyzed for pharmacokinetics, as well as for safety (adverse events and laboratory data). Frequency counts will be supplied for subject discontinuation(s) by hepatic function group.



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

8.2.2. Demographic and Clinical Examination Data

A break down of demographic data will be provided for age, race, weight, body mass index, and height. Each will be summarized by sex at birth and 'All Subjects' in accordance with the sponsor reporting standards.

8.2.3. Discontinuation(s)

Subject discontinuations, temporary discontinuations or dose reductions due to adverse events will be detailed and summarized by hepatic function group.

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

8.2.4. Adverse Events

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

8.2.5. Laboratory Data

The baseline measurement is the last predose measurement.

For each planned timepoint, baseline values and change from baseline values within each hepatic function group will be summarized with descriptive statistics (using sponsor default standards).

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

8.2.6. Vital Signs Data

Supine blood pressure and pulse rate will be measured as per the Schedule of Activities mentioned in the protocol.

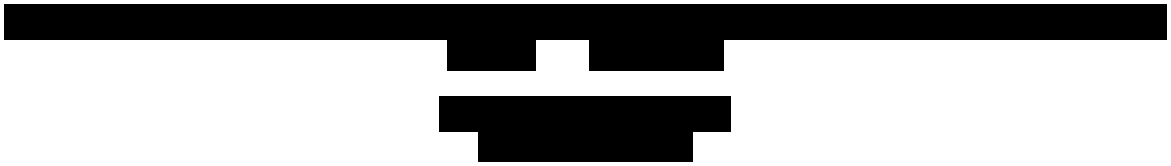
The baseline measurement is the last predose measurement.

For each planned timepoint, baseline values and change from baseline values within each hepatic function group will be summarized with descriptive statistics (using sponsor default standards).

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

8.2.7. ECG Data

The baseline measurement is the predose measurement.



Changes from baseline for the ECG parameters QT interval, heart rate, QTc interval, PR interval, and QRS complex will be summarized by cohort and time.

The number (%) of participants with maximum post-dose QTc values and maximum increases from baseline in the following categories will be tabulated by cohort:

Safety QTc Assessment

Degree of Prolongation	***Mild (msec)***	***Moderate (msec)***	***Severe (msec)***
Absolute value	*>450-480*	*>480-500*	*>500*
Increase from baseline		*30-60*	*>60*

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

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

8.2.8. Other Safety Data

None.

8.2.9. Concomitant Treatments

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

8.2.10. Screening and Other Special Purpose Data

Prior medication(s) and non-drug treatment(s), serum FSH concentrations, urine drug screen, serum or urine B-hCG for all females of childbearing potential, Alcohol/tobacco use and Breath alcohol test, Hepatitis B (HepBsAg, HepBcAb), Hepatitis C (HCVAb), and HIV tests and urine drug testing will be obtained at Screening.

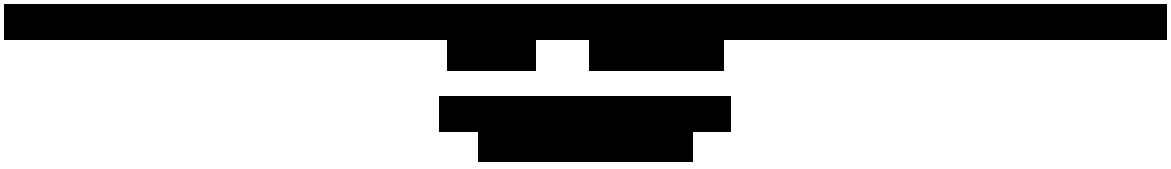
These data will not be brought in-house, and therefore will not be listed.

8.2.11. Other Analyses

PGx (pharmacogenomics) data will be collected and listed by subject per cohort in this study.

8.2.12. Child-Pugh Classification Data

This data will be listed by subject per cohort in this study.



9. REFERENCES

None.

[redacted]

10. APPENDICES

Appendix 1. SAS CODE FOR ANALYSES

An example of the PROC GLM code is provided below:

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

/* Letter assignments for group within the estimate statement above are as follows;

A = Severe hepatic impairment (Test)
B = Normal hepatic function (Reference);
  */;
```