Protocol *B7981016*

A PHASE 1, NON-RANDOMIZED, OPEN LABEL, MULTIPLE DOSE STUDY TO EVALUATE THE PHARMACOKINETICS, SAFETY AND TOLERABILITY OF PF-06651600 IN SUBJECTS WITH HEPATIC IMPAIRMENT AND IN HEALTHY SUBJECTS WITH NORMAL HEPATIC FUNCTION

Statistical Analysis Plan (SAP)

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

TABLE OF CONTENTS

LIST OF TABLES 4
LIST OF FIGURES 4
1. AMENDMENTS FROM PREVIOUS VERSION(S) 5
2. INTRODUCTION 5
2.1. Study Design 5
2.2. Study Objectives 8
3. INTERIM ANALYSES, FINAL ANALYSES AND UNBLINDING 9
4. HYPOTHESES AND DECISION RULES 9
4.1. Statistical Hypotheses 9
4.2. Statistical Decision Rules 9
5. ANALYSIS SETS 9
5.1. Pharmacokinetic (PK) Analysis Set 9
5.1.1. Concentration Analysis Set 9
5.1.2. Parameter Analysis Set 9
5.2. Pharmacodynamic Analysis Set 9
5.3. Safety Analysis Set 9
5.4. Other Analysis Sets 9
5.5. Treatment Misallocations 10
5.6. Protocol Deviations 10
5.6.1. Deviations Assessed Prior to Randomization 10
5.6.2. Deviations Assessed Post-Randomization 10
6. ENDPOINTS AND COVARIATES 10
6.1. Efficacy Endpoint(s) 10
6.2. Safety Endpoints 10
6.3. Other Endpoints 11
6.3.1. PK Endpoints 11
6.3.2. PD Endpoints 11
6.4. Covariates 11
7. HANDLING OF MISSING VALUES 11
7.1. Concentrations Below the Limit of Quantification 11
7.2. Deviations, Missing Concentrations and Anomalous Values 11
7.3. Pharmacokinetic Parameters 12

8. STATISTICAL METHODOLOGY AND STATISTICAL ANALYSES 12
8.1. Statistical Methods 12
8.2. Statistical Analyses 12
8.3. Safety Analysis 14
8.3.1. Treatment and Disposition of Subjects 14
8.3.2. Demographic and Clinical Examination Data 14
8.3.3. Discontinuation(s) 14
8.3.4. Adverse Events 15
8.3.5. Laboratory Data 15
8.3.6. Vital Signs Data 15
8.3.7. Physical Examination Data 15
8.3.8. ECG Data 15
8.3.9. Other Safety Data 15
8.3.10. Concomitant Treatments 15
8.3.11. Screening and Other Special Purpose Data 15
9. REFERENCES 16
10. APPENDICES 17

LIST OF TABLES

Table 1. Study Cohorts Based on Hepatic Function Categories 5
Table 2. Assessment of Hepatic Impairment: Child-Pugh Scale 5
Table 3. Determination of Encephalopathy Grade 6
Table 4. Noncompartmental PK Parameters 11
Table 5. PK Parameters to be Summarized Descriptively by Group 13

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LIST OF FIGURES

None.

APPENDICES

Appendix 1. SAS CODE FOR ANALYSES 17

1. AMENDMENTS FROM PREVIOUS VERSION(S)

None.

2. INTRODUCTION

PF-06651600 is a selective covalent inhibitor of Janus kinase (JAK) 3 (JAK3) and the tyrosine kinase expressed in hepatocellular carcinoma (TEC) family kinases and is currently under development for the treatment of alopecia areata (AA), rheumatoid arthritis (RA), vitiligo, ulcerative colitis (UC), and Crohn's Disease (CD).

The objective of this non-randomized, open label, multiple dose study is to characterize the effect of hepatic impairment on the pharmacokinetic(s) (PK) of PF-06651600 following administration of multiple 30 mg once daily (QD) doses of PF-06651600.

2.1. Study Design

This is a Phase 1 non-randomized, open-label, multiple-dose, parallel-cohort study to investigate the effect of hepatic impairment on the plasma PK, safety and tolerability of PF-06651600 after multiple oral doses of 30 mg QD. At Screening, the Child-Pugh classification score will be utilized to assess entry criteria and to assign participants into the appropriate hepatic-impairment group (Table 1, Table 2, and Table 3). The participants' hepatic function will be ranked based on clinical signs and liver function test (LFT) results.

Table 1. Study Cohorts Based on Hepatic Function Categories

Cohort	*Description*	*Child-Pugh Score*	*Number of Participants*
1	*Moderate hepatic impairment*	*Class B (7 to 9 points)*	*8*
2	*Normal hepatic function*	*Not Applicable*	*8*
3	*Mild hepatic impairment*	*Class A (5 to 6 points)*	*8*

Table 2. Assessment of Hepatic Impairment: Child-Pugh Scale

Assessment Parameters	*Assigned Score for Observed Findings*		
	1 point	*2 point*	*3 point*
Encephalopathy Grade	*0*	*1 or 2*	*3 or 4*
Ascites	*Absent*	*Slight*	*Moderate*
Serum total bilirubin (mg/dL)	*<2*	*2 to 3*	*>3*
Serum albumin (g/dL)	*>3.5*	*2.8 to 3.5*	*<2.8*
INR	*<1.7*	*1.7 to 2.3*	*>2.3*

Table 3. Determination of Encephalopathy Grade

Encephalopathy Grade	*Definition*
0	*Normal consciousness, behavior, personality, neurological examination, electroencephalogram.*
1	*Restless, sleep disturbed, irritable/agitated, tremor, impaired handwriting, 5 cycles persecond (cps) waves on EEG.*
2	*Lethargic, time-disoriented, hyperactive reflexes, rigidity, slow waves on EEG.*
3[a]	*Somnolent, stuporous, place-disoriented, hyperactive reflexes, rigidity, slow waves on EEG.*
4[a]	*Unrousable coma, no personality/behavior, decerebrate, slow 2-3 cps delta activity on EEG.*

a. Participants with clinically active Grade 3 or 4 encephalopathy are excluded.

***Part 1**: A total of approximately 16 participants will be enrolled in Part 1: 8 participants with moderate hepatic impairment and 8 healthy participants with normal hepatic function. Healthy participants with normal hepatic function will be enrolled after completion of moderate hepatic impairment participants and will be matched for age, weight, race, and gender to the mean demographics of participants in the moderate hepatic impairment group. Healthy normal participants will be enrolled to enable comparison of PK parameters between healthy participants and participants with moderate hepatic impairment.*

Reasonable efforts will be made to enroll an adequate number of participants (1 to 3 participants) with Child-Pugh scores of 8 and 9 to ensure that the entire range of moderate hepatic impairment is represented. Participants who withdraw from the normal and moderate impairment groups for non-safety related reasons and who are considered to be non-evaluable with respect to the primary PK objective will be replaced at the discretion of the sponsor such that the number of completed evaluable participants in each group equals eight.

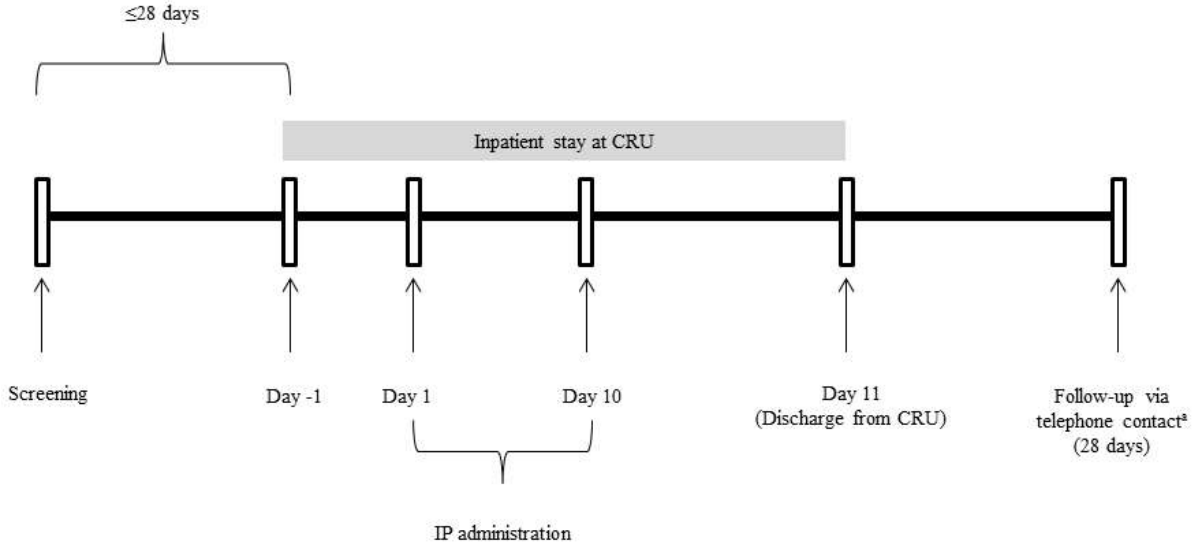
After evaluation of results from Part 1, Part 2 may be conducted if PF-06651600 area under the concentration-time curve from time zero to 24 hours (AUC_{0-24}) geometric mean ratio (GMR) for moderate hepatic impairment group compared to normal group is ≥2.0.

If the above mentioned criterion is not met, the study will stop after Part 1.

***Part 2**: Based on whether the decision criterion to proceed to Part 2 is met, approximately 8 participants with mild hepatic impairment will be enrolled. As in Part 1, hepatic impairment classification will be based on the Child-Pugh score. Healthy participants will not be enrolled in Part 2. When recruiting the Part 2 participants attempts to match the entire group with respect to age, gender and body weight to the participants in Part 1 will be made. Other demographics, such as race and ethnicity, may be considered for matching to the Cohort 1 and Cohort 2 population when possible.*

As in Part 1, participants who withdraw from the mild impairment group for non-safety related reasons and who are considered to be non-evaluable with respect to the primary PK objective will be replaced at the discretion of the sponsor such that the number of completed evaluable participants in the group equals 8.

For both Parts 1 and 2: *Screening will occur within 4 weeks of the first dose of study medication. All participants will provide informed consent and undergo Screening evaluations to determine their eligibility. Eligible participants will be admitted to the Clinical Research Unit (CRU) on Day -1 and will be confined in the CRU until Day 11. Safety assessments will be performed during screening, prior to dosing on Day -1, Day 5 and Day 11. Participants will have a follow-up phone call 28+3 days after last dose administration to assess for AEs. Overall study design is summarized* in the figure below.



Abbreviations: CRU = clinical research unit; IP = investigational product.

a. *Follow-up telephone contact may occur as onsite visit for follow-up of clinically significant abnormal laboratory tests and/or ongoing AEs and must occur 28+3 days from administration of the final dose of investigational product.*

The study is designed as a parallel cohort, open label study to investigate the effect of hepatic impairment on the PK of PF-06651600. The cohort of healthy participants will be served as a control group for the cohort/s with hepatic impairment. The study is designed as a 2-part study where participants with moderate hepatic impairment and normal hepatic function will be evaluated first in Part 1. Participants with mild hepatic impairment will be evaluated in Part 2 only if the results from Part 1 indicate that a dose adjustment may be required for participants with moderate hepatic impairment (ie, GMR ≥2.0).

The study will evaluate the multiple dose PK of PF-06651600 in healthy and hepatically impaired participants. Multiple doses are used to allow concentrations to achieve steady state, since PF-06651600 may have non-stationary PK due to time dependant inhibition and/or induction of CYP3A.

The study will use the PF-06651600 dose of 30 mg (3 × 10 mg tablets) QD, given orally for up to 10 days. The 30 mg dose of PF-06651600 is a clinically relevant dose of PF-06651600 used in efficacy and safety trials. The 30 mg dose of PF-06651600 is also appropriate considering that hepatic impairment is expected to increase the systemic exposures of PF-06651600.

A participant is considered to have completed the study if he/she has completed all phases of the study including the last visit (Follow-up Phone Contact) and the investigator has reviewed the final safety data and determined that no additional evaluation is required.

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

Part 1

Primary Objective

- *To estimate the effect of moderate hepatic impairment on the PK of PF-06651600 following multiple dose administration.*

Secondary Objective

- *To evaluate safety and tolerability of multiple doses of PF-06651600.*

Tertiary/Exploratory Objective

- *To estimate the effect of moderate hepatic impairment on additional PK parameters of PF-06651600.*

Part 2 (if applicable)

Primary Objective

- *To estimate the effect of mild hepatic impairment on the PK of PF-06651600 following multiple dose administration.*

Secondary Objective

- *To evaluate safety and tolerability of multiple doses of PF-06651600.*

Tertiary/Exploratory Objective

- *To estimate the effect of mild hepatic impairment on additional PK parameters of PF-06651600.*

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.

Prior enrollment of normal subjects in Part 1, summary of demographic data for moderate subjects will be provided.

Additionally, PK data will be analyzed upon completion of Part 1 and based on the results decision will be made whether to progress to Part 2. If decision will be made to progress to Part 2, demography data from Part 1 will be summarized to guide enrollment in Part 2.

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

The PK concentration population is defined as all participants treated who have at least 1 concentration.

5.1.2. Parameter Analysis Set

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

5.2. Pharmacodynamic Analysis Set

None.

5.3. Safety Analysis Set

All participants assigned to investigational product and who take at least 1 dose of investigational product. Participants will be analyzed according to the product they actually received.

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 enrolled 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 (eg, 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 4.1 and 4.2 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.

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,*
- *physical examination data,*

- *ECG results.*

6.3. Other Endpoints

6.3.1. PK Endpoints

Blood samples for PK analysis of PF-06651600 will be taken according to the Schedule of Activities given in the protocol.

The following PK parameters will be calculated for PF-06651600 (if possible) from the concentration-time data using standard noncompartmental methods:

Table 4. Noncompartmental PK Parameters

PK Parameter	Analysis Scale	PF-06651600
AUC_{0-24}	ln	A, D
AUC_{last}	ln	D
C_{max}	ln	A, D
T_{max}	R	D
CL/F*	ln	D
C_{trough}	R	D

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

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 groups) and the Reference (normal hepatic function group) using a one-way ANOVA model based on natural log transformed data.

8.2. Statistical Analyses

Analysis of variance (ANOVA) will be used to compare the natural log transformed

PF-06651600 AUC_{0-24} and maximum plasma concentration (C_{max}) between normal hepatic function group (Reference) and the moderate impaired hepatic function group (Test). Estimates of the adjusted mean differences (Test-Reference) and corresponding 90% confidence intervals (CIs) will be obtained from the model. The mean differences and 90% CIs for the differences will be exponentiated to provide estimates of the ratio of the geometric means (Test/Reference) and 90% CIs for the ratios.

Part 2 may be conducted if PF-06651600 AUC_{0-24} geometric mean ratio for moderate hepatic impairment group compared to normal group is ≥2.

Part 2

ANOVA will be used to compare the natural log transformed PF-06651600 AUC_{0-24} and C_{max} between normal hepatic function group (Reference) and the moderate and mild impaired hepatic function groups (Tests). Estimates of the adjusted mean differences (Test-Reference) and corresponding 90% CIs will be obtained from the model. The mean differences and 90% CIs for the differences will be exponentiated to provide estimates of the ratio of the geometric means (Test/Reference) and 90% CIs for the ratios.

Box and whisker plots for individual participant parameters (AUC_{0-24} and C_{max}) will be constructed by hepatic function group and overlaid with geometric means.

For summary statistics and median/mean plots by sampling time, the nominal PK sampling time was 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 by hepatic function group:

Table 5. PK Parameters to be Summarized Descriptively by Group

Parameter	Summary Statistics
AUC_{0-24}, AUC_{last}, C_{max}, C_{trough}, CL/F	N, arithmetic mean, median, cv%, standard deviation, minimum, maximum, geometric mean and geometric cv%.
T_{max}	N, median, minimum, maximum.

Presentations for PF-006651600 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).

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.

8.3. Safety Analysis

All participants assigned to investigational product and who take at least 1 dose of investigational product. Participants will be analyzed according to the product they actually received.

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-06651600.

8.3.1. 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.

8.3.2. Demographic and Clinical Examination Data

A break-down of demographic data will be provided for each hepatic function group 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.

8.3.3. 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.

8.3.4. Adverse Events

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

8.3.5. Laboratory Data

The baseline measurement is the last predose measurement.

These data will be listed and frequencies of out of range values will be provided in accordance with the sponsor reporting standards.

8.3.6. Vital Signs Data

The baseline measurement is the last pre-dose measurement.

These data will be listed and frequencies of out of range values will be provided in accordance with the sponsor reporting standards.

8.3.7. Physical Examination Data

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

8.3.8. ECG Data

ECG data will be listed and frequencies of out of range values will be provided in accordance with the sponsor reporting standards.

8.3.9. Other Safety Data

None.

8.3.10. Concomitant Treatments

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

8.3.11. Screening and Other Special Purpose Data

Listing of Child-Pugh Score (along with any collected sub scores) will be provided. 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 & breath alcohol test, HIV, HBsAg, HBcAb, HCVAb, QFT-G Test or PPD skin test will be obtained at Screening.

If these data are brought in-house, then they will be listed.

9. REFERENCES

None.

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/ S covb alpha=0.1 CL DDFM=KR;
        repeated/ type=un subject=subjid group=group R;
        lsmeans group;
        estimate 'Moderate vs Normal'          group  1 -1 ;

        *****If Part 2 is conducted then *******;
        estimate 'Moderate vs Normal'          group  1 -1 0;
        estimate 'Mild vs Normal'              group  0 -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 = Moderate (Test);
B = Normal (Reference);
C = Mild (Test);
  */;
```