Protocol *B7931048*

A PHASE 1, NON-RANDOMIZED, OPEN LABEL, SINGLE DOSE STUDY TO EVALUATE THE PHARMACOKINETICS, SAFETY AND TOLERABILITY OF PF-06700841 IN PARTICIPANTS WITH RENAL IMPAIRMENT AND IN HEALTHY PARTICIPANTS WITH NORMAL RENAL FUNCTION

Statistical Analysis Plan (SAP)

Version: 1.0

SAP Author: PPD (FSP Statistician – PPD)

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Revision History

Version	Date	Author(s)	Summary of Changes/Comments
1.0	February 18, 2020	PPD	Not Applicable

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

[redacted]

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APPENDICES

1. AMENDMENTS FROM PREVIOUS VERSION(S)

None.

2. INTRODUCTION

PF-06700841 is a potent tyrosine kinase 2 (TYK2)/Janus kinase (JAK) 1 inhibitior that is currently being developed for the treatment of patients with inflammatory diseases, including systemic lupus erythematosus (SLE), psoriatic arthritis (PsA), psoriasis (PsO), alopecia areata (AA), vitiligo, inflammatory bowel disease (IBD), hidradenitis suppurativa (HS) and atopic dermatitis (AD).

PF-06700841 is intended for chronic use in patients, some of whom may have some degree of impaired renal function. Therefore, the purpose of this study is to characterize the effect of renal impairment on the plasma PK of PF-06700841. Findings from this study will be used to develop dosing recommendations so that the dose and/or dosing interval may be adjusted appropriately in the presence of renal disease.

2.1. Study Design

This is a Phase 1, non-randomized, open-label, single-dose, parallel-cohort study to investigate the effect of renal impairment on the plasma PK, safety and tolerability of PF-06700841 after single oral dose of 30 mg. A staged approach, as outlined in detail below, will be followed in the study. Participants will be selected and categorized into normal renal function or renal impairment groups based on their estimated glomerular filtration rate (eGFR) as shown in Table 1.

Table 1. Renal Function Categories by eGFR Ranges

Cohort	*Renal Impairment* [a]	*Estimated eGFR* [b] *(mL/min))*	*Number of Participants*
1	*Severe renal impairment*	*<30 and not requiring dialysis*	*8*
2	*Normal renal function*	*≥90*	*8*
3	*Moderate renal impairment*	*≥30 to <60*	*8*
4	*Mild renal impairment*	*60 – 89*	*8*

a. *Stages of renal impairment are based on Kidney Disease Outcomes Quality Initiative (KDOQI) Clinical Practice Guidelines for Chronic Kidney Disease (CKD).*[1]

b. *Estimate of eGFR based on Modification of Diet in Renal Disease (MDRD) formula. The average of the 2 screening eGFR value will be used for group assignment:*

- *Step 1: eGFR (mL/min/1.73 m^2) = 175 × $(Scr, _{std})^{-1.154}$ × $(Age)^{-0.203}$ × (0.742 if female) × (1.212 if African American) where $Scr, _{std}$ denotes serum creatinine measured with a standardized assay.*
- *Step 2: Convert the MDRD-derived, body surface area (BSA)-adjusted eGFR obtained above to absolute eGFR (mL/min) for eligibility assessment using the following equation: eGFR (mL/min) = eGFR (mL/min/1.73 m^2) × participant's BSA where BSA is calculated as BSA= $(Weight^{0.425} \times Height^{0.725})$ × 0.007184.*

Part 1*: A total of approximately 16 participants will be enrolled in Part 1; approximately 8 participants with severe renal impairment (Cohort 1) and approximately 8 with normal renal function (Cohort 2) to ensure at least 6 evaluable participants in each group. Participants from the severe renal impairment group will be recruited first. The demographics will be pooled across study sites to determine an average value for age and weight in the severe impairment group. Subsequently, the healthy participants will be recruited later such that each participant's age is within ±10 years and weight is within ±15 kg of the mean of severe renal impairment group. An attempt will be made to maintain a similar male/female ratio composition between groups. Care will be taken when recruiting the healthy participants such that the entire group is not of substantially different age or of substantially different body weight than the severely renally impaired participants. Approval from the sponsor must be obtained* ***before*** *proceeding with dosing healthy participants with normal renal function.*

If there are participants who withdraw or discontinue treatment from the normal or severe renal impairment groups and who are considered to be non-evaluable with respect to the primary PK objective, additional participants can be enrolled at the discretion of the sponsor.

Criteria to proceed to Part 2: After statistical evaluation of results from Part 1 (see- study protocol *Section 9.4), Part 2 will be conducted if the point estimate of PF-06700841 or M1 area under the concentration-time curve from time 0 to infinity (AUC_{inf}) geometric mean ratio (GMR) for the severe renal impairment group (compared to the normal group as control) is ≥1.5. If this 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 each with moderate (Cohort 3) and mild (Cohort 4) renal impairment will be enrolled to ensure at least 6 evaluable participants in each group. As in Part 1, renal impairment classification will be based on eGFR. Healthy participants will not be enrolled in Part 2. Healthy participants from Part 1 will be used as the control group for the moderate and mild impairment participants.*

When recruiting the Part 2 participants, attempts to match the entire group to the participants in Part 1 with respect to age, gender and body weight will be made. Other demographics, such as race and ethnicity, may be considered for matching the Part 1 and Part 2 populations when possible. Statistical considerations to account for any differences in demographics are detailed in study protocol *Section 9.4.*

As in Part 1, if there are participants who withdraw or discontinue treatment from the moderate or mild impairment group and who are considered to be non-evaluable with respect to the primary PK objective, additional participants can be enrolled at the discretion of the sponsor.

For both Parts 1 and 2*: All participants in both normal and renal impairment groups will provide informed consent and undergo Screening evaluations to determine their eligibility. Participant screening for participation in this study will consist of 2 CRU outpatient visits not more than 14 days apart (but at least 3 days apart), with the 1st screening visit occurring within 28 days prior to administration of investigational product. Each participant will be admitted to the research unit on Day -1 (at least 12 hours prior to the dosing of PF-06700841 on Day 1). An eGFR value for group placement (provided stable renal function is still demonstrated) will be obtained by the average of the 2 screening values (using the Modification of Diet in Renal Disease [MDRD] equation). If the renal function stability criterion is met but the renal function classification category changes between Screening Visit 1(S1) eGFR and the average of the S1 and Screening Visit 2 (S2) eGFRs, the eGFR measurement at Day -1 will also be used to determine the appropriate group classification category using an average of all 3 eGFR values, to determine whether the participant will be eligible for enrollment.*

All procedures and their timelines follow the Study Protocol' *Schedule of Activities.*

Calculation of eGFR:

The following MDRD equation will be used to calculate eGFR (Scr, $_{std}$ denotes serum creatinine measured with a standardized assay for serum creatinine):

$$eGFR\ (mL/min/1.73m^2) = 175 \times (Scr,_{std})^{-1.154} \times (Age)^{-0.203} \times (0.742\ \text{if female}) \times (1.212\ \text{if African American})$$

Note that the value of eGFR, which is directly obtained from the laboratory or calculated using the equation above, is generally normalized to an average body size of 1.73 m^2 for diagnosis, prognosis and treatment of renal disease. In terms of clearance of renally filtered drugs (including secreted drugs), renal elimination capacity is related to absolute glomerular filtration rate (GFR) in mL/min. To use the MDRD-derived, body surface area (BSA)-adjusted value of eGFR to obtain absolute glomerular filtration rate (GFR) (mL/min) for renal disease classification or participant assignment into different renal disease groups, this value should be multiplied by the individual participant's BSA (ie, measured BSA/1.73 m^2). The BSA of an individual can be calculated by the following formula as described below:

$$BSA = (Weight^{0.425} \times Height^{0.725}) \times 0.007184$$

In summary, GFR in mL/min calculated as below will be used for renal impairment group placement:

<u>Step 1</u>: Obtain the MDRD-derived eGFR:

- ***eGFR (mL/min/1.73 m^2)*** *= $175 \times (Scr,_{std})^{-1.154} \times (Age)^{-0.203} \times (0.742\ \text{if female}) \times (1.212\ \text{if African American})$ where Scr, $_{std}$ denotes serum creatinine measured with a standardized assay.*

Step 2: Convert the MDRD-derived, BSA-adjusted eGFR obtained above to absolute GFR (mL/min) for eligibility assessment using the following equation:

- ***eGFR (mL/min)** = eGFR (mL/min/1.73 m^2) × participant's BSA where BSA is calculated as BSA = (Weight$^{0.425}$ × Height$^{0.725}$) × 0.007184.*

Creatinine clearance (CL_{CR}) will also be estimated from a spot serum creatinine measurement using the following Cockcroft-Gault (C-G) equation:

$$CL_{CR}\ (mL/min) = (140 - age\ [years]) \times total\ body\ weight\ (kg) \times (0.85\ for\ females) \div (72 \times serum\ creatinine\ (mg/dL))$$

Note that eGFR calculated by the MDRD equation will be used for categorization of degrees of renal impairment. Nevertheless, renal function will be estimated using both C-G and MDRD equations in this study and dose recommendations will be made using both C-G and MDRD equations.

To be enrolled into the study, participant must demonstrate stable renal function, with ≤25% change based upon screening S1 eGFR and screening S2 eGFR (calculated by the MDRD equation). The S2 eGFR assessment should be performed between 3 to 14 days after the S1 eGFR assessment. The average of these 2 eGFR values will be used for group placement based on the renal function classification category.

- *If the renal function stability criterion is met and the renal function classification category remains the same between S1 eGFR and the average of the S1 and S2 eGFRs, participant will be eligible for enrollment.*

- *If the renal function stability criterion is not met, participant will be screen failed.*

- *If the renal function stability criterion is met but the renal function classification category changes between S1 eGFR and the average of the S1 and S2 eGFRs, the eGFR measurement at Day -1 will also be used to determine the appropriate group classification category using an average of all 3 eGFR values, to determine whether the participant will be eligible for enrollment.*

In case of screen failure related to eGFR stability and/or change in the renal function classification category, participant may be re-screened once after a 30-day period, provided that the initial screen failure is not due to an Inclusion/Exclusion criterion that results in permanent disqualification from enrollment (eg, medical history). This can be done only with sponsor's approval.

Please see below table regarding demonstration of stable renal function:

Renal function Measurement	*eGFR (mL/min)*	*Criterion for stability*
S1	*G1*	
S2 (Within 3 to 14 days after S1)	*G2*	$\Delta = \lvert G2-G1 \rvert \times 100/G1$[a] *If* $\Delta \leq$ *25%; stable* *If* $\Delta >$*25%; not stable*

Abbreviations: S1= Screening Visit 1; S2= Screening Visit 2.

[a] *Parenthesis of | | represents absolute values.*

2.2. Study Objectives

Primary:

- *Part 1: To evaluate the effect of severe renal impairment on the PK of PF-06700841 and M1, a major metabolite of PF-06700841, following single oral dose administration.*
- *Part 2 (if applicable): To evaluate the effect of moderate and mild renal impairment on the PK of PF-06700841 and M1 following single oral dose administration.*

Secondary:

- *To evaluate the safety and tolerability of single oral dose of PF-06700841 in participants with renal impairment and in healthy participants with normal renal function.*

CCI

[redacted]

3. INTERIM ANALYSES, FINAL ANALYSES AND UNBLINDING

No formal interim analysis will be conducted for this study. The data will be reviewed after completion of Part 1 in order to determine whether Part 2 will proceed. Final analysis will follow the official database release. As this will be an open, nonrandomized study, there is no formal unblinding.

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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 assigned to investigational product and treated who have at least 1 concentration measured.

5.1.2. Parameter Analysis Set

The PK parameter analysis population is defined as all participants assigned to investigational product and treated who have at least 1 of the PK parameters of primary interest measured.

5.2. Pharmacodynamic Analysis Set

None.

5.3. Safety Analysis Set

All assigned to investigational product and who take at least 1 dose of investigational product.

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 participants who are randomized but not treated.

If a participant takes a treatment that is not consistent with the treatment they are randomized to, for example 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

Participants 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 participants 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.

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,*
- *Physical Examination.*

6.3. Other Endpoints

6.3.1. PK Endpoints

Blood and urine samples for PK analysis of PF- 06700841 and M1 will be taken according to the Schedule of Activities given in the protocol.

The following PK parameters will be calculated for PF- 06700841 and M1 (if possible) from the concentration-time data using standard non compartmental methods:

Table 2. Noncompartmental PK Parameters

Matrix	PK Parameter	Analysis Scale	PF-06700841	M1
Plasma	AUC_{inf}*	ln	A, D	A, D
	CCI			
	AUC_{72}	ln	A, D	A, D
	C_{max}	ln	A, D	A, D
	CCI			
Urine	CL_R	ln	A, D	A, D
	Ae72	R	D	D
	Ae72(%)	R	D	D

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

- Urine samples will be analyzed only if it is determined by the study team that there is a need to do so based on the review of plasma PK results for PF-06700841 and M1 (as per study protocol Section 8.5.2).

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 participant's concentration data, the parameter will be coded as NC (i.e. 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 renal function group with ≥3 evaluable measurements. For statistical analyses (i.e. 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.

8. STATISTICAL METHODOLOGY AND STATISTICAL ANALYSES

8.1. Statistical Methods

Part 1, the effect of the severe renal impairment on PK parameters will be assessed by constructing 90% confidence intervals around the estimated difference between the severe renal impairment and the normal renal function using a one-way ANOVA model based on natural log transformed data.

Following Part 2 (if conducted), the same ANOVA analysis will be performed using data from the mild and moderate renal impairment groups.

Part 2 may be conducted if either PF-06700841 or M1 AUC_{inf} GMR for severe renal impairment group compared to normal group is ≥1.5 in Part 1.

The relationship between PK parameters [CCI] or renal clearance [CLr], [CCI]) and renal function will be determined by a linear regression model for PF-06700841 and M1, if Part 2 is conducted, and for the PF-06700841.

8.2. Statistical Analyses

Part 1

Analysis of variance (ANOVA) will be used to compare the natural log transformed AUC_{inf} and C_{max} for PF-06700841 and M1 between normal renal function group (Reference) and the severe impaired renal function group (Test). Estimates of the adjusted mean differences (Test-Reference) and corresponding 90% confidence intervals (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 the adjusted geometric means (Test/Reference) and 90% CIs for the ratios.

Part 2

Part 2 may be conducted if either PF-06700841 or M1 AUC_{inf} GMR for severe renal impairment group compared to normal group is ≥1.5 in Part 1.

ANOVA will be used to compare the natural log transformed AUC_{inf} and C_{max} for PF-06700841 and M1 between normal renal function group (Reference) and the moderate and mild impaired renal function groups (Test). 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 the adjusted geometric means (Test/Reference) and 90% CIs for the ratios. If substantial differences in demographic characteristics between healthy and impaired participants are observed, weight and age may be explored as covariates.

If Part 2 is executed and data for normal, mild, moderate and severe impairment groups are available, additional analysis will be performed to assess relationship between appropriate PK parameters and renal function.

Linear regression will be used to analyze the potential relationship between appropriate PK parameters ([CCI] or renal clearance [CLr], [CCI]) and renal function (eGFR). Estimates of the slope and, intercept, together with their precision (90% CI), and the coefficient of determination will be obtained from the model.

Plots of PK parameters (CCI or CLr, CCI) versus renal function (eGFR) will be constructed. A regression line and 90% confidence region for the PK parameters and eGFR will be included if appropriate. Vertical lines for the renal function group cut-off values will also be presented on the plots.

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 renal function group:

Table 3. PK Parameters to be Summarized Descriptively by Group

Parameter	Summary Statistics
AUC_{inf}, CCI AUC_{72}, C_{max}, CL_R, CCI CCI	N, arithmetic mean, median, cv%, standard deviation, minimum, maximum, geometric mean and geometric cv%.
CCI	[redacted]
CCI Ae_{72} and Ae_{72}%	N, arithmetic mean, median, cv%, standard deviation, minimum, maximum.

Box and whisker plots for individual participant parameters (AUC_{inf}, CCI AUC_{72} *and C_{max}) will be constructed by renal function group and overlaid with geometric means.*

Supporting data from the estimation of CCI 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 *PF-06700841 and M1* concentrations will include:

- A listing of all concentrations sorted by renal 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 renal 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 renal function group (all renal function groups on the same plot per scale, based on the summary of concentrations by renal function group and time postdose).

- Mean concentrations time plots (on both linear and semi-log scales) against nominal time postdose by renal function group (all renal function groups on the same plot per scale, based on the summary of concentrations by renal function group and time postdose).

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

- A listing of all urine concentration interval sorted by renal function group (present in heading), subject ID and nominal collection duration postdose.

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

A set of summary tables split by renal function group will be produced to evaluate any potential risk associated with the safety and toleration of administering *PF-06700841.*

8.3.1. Treatment and Disposition of Participants

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

8.3.2. Demographic and Clinical Examination Data

Demographic data will be summarized by sex at birth and ‘All Participants’ in accordance with the sponsor reporting standards.

8.3.3. Discontinuation(s)

Participant discontinuations, temporary discontinuations due to adverse events will be detailed and summarized by renal function group.

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

8.3.4. Adverse Events

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

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

8.3.5. Laboratory Data

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

For laboratory parameters which are collected only at Screening for inclusion/exclusion criteria, data will not be captured for inclusion into the study database and therefore will not be listed or summarized.

Baseline is defined as the last planned predose measurement taken on Day -1.

8.3.6. Vital Signs Data

Supine measurements of BP, pulse rate, and oral temperature will be taken at times detailed in the Schedule of Activities given in the protocol.

Vital Signs will be assessed against the criteria specified in the sponsor reporting standards.

Baseline is defined as the last planned predose measurement taken on Day 1.

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

8.3.7. ECG Data

ECG data will be taken at times detailed in the Schedule of Activities given in the protocol.

Baseline is defined as the last planned predose measurement taken on Day 1.

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

8.3.8. Physical Examination

Physical examination data will be taken at times detailed in the Schedule of Activities given in the protocol.

These data will be listed and summarized 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

Prior medication(s) and non-drug treatment(s), HIV, HBsAg, HBcAb, HCVAb, urine drug screen, urine or serum pregnancy test (WOCBP only), Illegal drug/tobacco/alcohol use will be obtained at Screening.

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

9. REFERENCES

1. FDA Guidance for Industry – Pharmacokinetics in Patients with Impaired Renal Function - Study Design, Data Analysis, and Impact on Dosing and Labeling. 05/98.

10. APPENDICES

Appendix 1. SAS CODE FOR ANALYSES

For Part 1:

An example of the PROC MIXED code is provided below:

```
proc mixed data = tab.pk covtest alpha=0.1;
        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 'Severe vs Normal'             group -1  1;
        ods output lsmeans = lsmeans&var;
        ods output solutionf = solution&var;
run;

/* Letter assignments for group within the estimate statement above are as follows;
A = Normal (Reference), B = Severe (Test);*/;
```

For Part 2:

```
proc mixed data = tab.pk covtest alpha=0.1;
        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 'Mild vs Normal' group -1 1 0;
        estimate 'Moderate vs Normal' group -1 0 1;
        ods output lsmeans = lsmeans&var;
        ods output solutionf = solution&var;
run;

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

A = Normal (Reference), C = Moderate (Test), D = Mild (Test);

Severe group is not included */;
```

An example of the PROC REG code is provided below:

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

Note: Similar code will be used for regression analysis with respect to CCI and eGFR.