Protocol *B5341002*

A PHASE 1, OPEN-LABEL, RANDOMIZED, 2-TREATMENT SINGLE-DOSE, CROSS-OVER STUDY, 2-PART DESIGN TO EVALUATE THE BIOEQUIVALENCE AND TOLERABILITY OF TESTOSTERONE CYPIONATE FOLLOWING INTRAMUSCULAR (IM) INJECTION IN HEALTHY HYPOGONADAL MALE SUBJECTS

Statistical Analysis Plan (SAP)

Version: 2.0

SAP Author: PPD

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1. AMENDMENTS FROM PREVIOUS VERSION(S)

Revision History

Version	Date	Author(s)	Summary of Changes/Comments
2.0	April 10, 2020	PPD	The changes are reflecting as per the Protocol Amendment #3 dated 06 August 2019. • Title changed to remove 2-Period. • Section 2.1: Study Design is updated for Part 2. • Section 3: Interim Analyses plan is updated. • Section 4.2: Statistical Decision rules are updated. • Section 8: Statistical analyses are updated. • References are added. • Appendix is updated for Part 2 and adding the SAS code for reference Scaled Average Bioequivalence.
1.0	May 06, 2019	PPD	Not Applicable

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

2. INTRODUCTION

The current study will be assessing the BE between the current formulation (Reference formulation) and the reformulated presentation of testosterone cypionate injection (Test formulation) at a single 200 mg IM dose administered deep in the gluteal muscle. Since endogenous testosterone can interfere with the interpretation of systemic testosterone levels, the study will be conducted in hypogonadal males defined as subjects having serum testosterone levels below 2.5 ng/mL (250 ng/dL).

Overall, the study design incorporates 2 parts. As the variability associated with the PK of the reformulated presentation of testosterone cypionate solution for injection is unknown, Part 1 will assess the variability associated with exposures after administration of both the current formulation and reformulated presentation of testosterone cypionate solution for injection. Part 2 will evaluate the BE between both test and reference treatments.

2.1. Study Design

This is an open-label, randomized, 2-treatment, single-dose, cross-over study, 2-part design to evaluate the BE and tolerability of testosterone cypionate solution for injection (IM) administration in healthy hypogonadal male subjects (ages of 18 to 65 years). In Part 1, approximately 12 subjects will be enrolled in the study to ensure 10 evaluable subjects are to be randomized according to a computer-generated randomization schedule to receive the following 2 treatments below in random order.

***Treatment A**: A single testosterone cypionate solution for injection (new formulation) 200 mg dose administered IM deep in the gluteal muscle (Test).*

***Treatment B**: A single testosterone cypionate solution for injection (currently marketed formulation) 200 mg dose administered IM deep in the gluteal muscle (Reference).*

In Part 2, the observed variability associated with Cmax and AUC as well as the point estimates obtained from Part 1, were used to estimate the sample size needed to attain bioequivalence (BE) in Part 2. In Part 2, it is anticipated that approximately 60 subjects will be enrolled to ensure 57 evaluable subjects. Subjects will be randomized according to a computer-generated randomization schedule to receive the 2 treatments (eg, same as listed in Part 1) in a random order.

CCI [redacted]

Table 1. Study Schematics

Part 1 (12 subjects)[a]					
Sequence	***Period 1***	***Washout Period***	***Period 2***		
1 (6 subjects)	*Test treatment*	*At least 45 days*	*Reference treatment*		
2 (6 subjects)	*Reference treatment*		*Test treatment*		
Part 2 (60 subjects)[b]					
Sequence	***Period 1***	***Washout Period***	***Period 2***	***Washout Period***	***Period 3***
1 (20 subjects)	*Test treatment*	*At least 45 days*	*Reference treatment*	*At least 45 days*	*Reference treatment*
2 (20 subjects)	*Reference treatment*		*Test treatment*		*Reference treatment*
3 (20 subjects)	*Reference treatment*		*Reference treatment*		*Test treatment*

a. In Part 1, approximately 12 subjects will be enrolled to ensure 10 evaluable subjects.

b. In Part 2, approximately 60 subjects will be enrolled to ensure 57 evaluable subjects.

On Day 1, subjects will receive a single IM dose of either Test or Reference treatment according to randomization code. There will be at least a 45-day washout period between administration of each study medication in both Parts 1 and 2.

For Part 1, each subject will participate in the study with the duration of approximately 19 weeks from the time the subject signs the informed consent form through the final contact/follow-up contact.

For Part 2, each subject will participate in the study with the duration of approximately 25 weeks from the time the subject signs the informed consent form through the final contact/follow-up contact.

2.2. Study Objectives

Part 1

Primary Objective

- *To estimate the exposure variability of the test and reference formulations of testosterone cypionate solution for injection (200 mg) given intramuscularly as a single dose.*

Other Objective

- *To evaluate the safety and tolerability of testosterone cypionate solution for injection (200 mg).*

Part 2

Primary Objective

- *To evaluate the BE of the new formulation (testosterone cypionate solution for injection; 200 mg) relative to the currently marketed formulation (testosterone cypionate solution for injection; 200 mg) administered intramuscularly as a single dose.*

Other Objective

- *To evaluate the safety and tolerability of testosterone cypionate solution for injection (200 mg) following a single dose IM administration.*

3. INTERIM ANALYSES, FINAL ANALYSES AND UNBLINDING

No formal interim analysis will be conducted for this study. However, 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-escalation decisions, facilitating PK/pharmacodynamic (PD) modeling, and/or supporting clinical development. Final PK analysis of Part 1 will be conducted prior to the start of Part 2 to potentially further refine the sample size calculation and confirm the current study design of Part 2. If results from Part 1 depict within-subject variability ≥30% (eg, highly variable drug), the study design and/or methodology of data analysis may be modified.

Based on the results from Part 1, when the bioequivalence estimation was performed without the baseline correction, test formulation (Treatment A) was found to be bioequivalent to reference formulation (Treatment B) for AUC_{inf}, AUC_{last} and C_{max}. For all PK parameters the 90% CI for the ratio of the adjusted geometric mean fell within the 80-125% limits. However, when the data was analyzed with baseline testosterone correction, the 90% CI for the ratio for all the PK parameters was outside the 80%-125% limit. Importantly, the variability associated with AUC_{inf} was approximately 40%. The higher variability observed in these results as compared to the previous B5341001 study is the reason for the change in the original design of Part 2 from a 2-period crossover to a partial replicate design involving 3 periods.

4. HYPOTHESES AND DECISION RULES

No formal statistical hypotheses will be tested using the data obtained from Part 1 of this study.

4.1. Statistical Hypotheses for Part 2

The alternative hypothesis of bioequivalence (H1: θL <=μT - μR <=θU), and the null hypothesis of inequivalence (Ho: μT - μR <θL or μT - μR >θU) can be expressed as the following two separate one-sided hypotheses:

HoA: μT - μR <θL

H1A: θL <=μT - μR

HoB: μT - μR >θU

H1B: μT - μR <=θU

where μT and μR represent the average bioavailability on a log scale for the Test and Reference products respectively and [θL, θU] defines the bioequivalence range.

4.2. Statistical Decision Rules for Part 2

For AUC_{inf} (if data permit, otherwise AUC_{last}) and C_{max}, either average bioequivalence or reference scaled average bioequivalence will be used for determining bioequivalence. The method to be used is determined by the within-subject standard deviation of the Reference product for each parameter separately.

Bioequivalence will be demonstrated if both AUC_{inf} and C_{max} meet the conditions of bioequivalence using their respective method outlined in Sections 4.2.1 and 4.2.2.

4.2.1. Average Bioequivalence Decision Rules

Average bioequivalence (within-subject standard deviation of the reference <0.294):

The two one-sided hypotheses are tested at the α= 0.05 levels of significance for log-transformed AUC_{inf} (if data permit, otherwise AUC_{last}) and C_{max} by constructing the 90% confidence interval for the ratio between the test and reference geometric means.

Bioequivalence will be demonstrated if the estimated 90% confidence interval for the ratios (Test/Reference) of adjusted geometric means for AUC_{inf} (if data permit, otherwise AUC_{last}) and/or C_{max} fall entirely within (80%, 125%).

4.2.2. Reference Scaled Average Bioequivalence Decision Rules

The one-sided hypothesis will be tested at the α= 0.05 levels of significance for log-transformed AUC_{inf} (if data permit, otherwise AUC_{last}) and C_{max} by constructing the upper bound of the 95% confidence interval for

$$(\bar{Y}_T - \bar{Y}_R)^2 - \left(\frac{\ln(1.25)}{0.25}\right)^2 s^2_{WR}.$$

Bioequivalence will be demonstrated if the upper bound of the estimated 95% confidence interval for

$$(\bar{Y}_T - \bar{Y}_R)^2 - \left(\frac{\ln(1.25)}{0.25}\right)^2 s^2_{WR}$$

is less than zero (0) and the point estimate of the ratios (Test/Reference) of adjusted geometric means for AUC_{inf} (if data permit, otherwise AUC_{last}) and/or C_{max} fall within (80%, 125%).

5. ANALYSIS SETS

5.1. Pharmacokinetic (PK) Analysis Set

5.1.1. Concentration Analysis Set

The PK concentration population is defined as all subjects randomized and treated who have at least 1 concentration in at least 1 treatment period.

5.1.2. Parameter Analysis Set

The PK parameter analysis population is defined as all subjects randomized and treated who have at least 1 of the PK parameters of primary interest in at least 1 treatment period.

5.2. Pharmacodynamic Analysis Set

None.

5.3. Safety Analysis Set

All subjects who receive at least 1 dose of study medication will be included in the safety analyses and listings.

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 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 and PK 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.

CCI [redacted]

6.3. Other Endpoints

6.3.1. PK Endpoints

Blood samples for PK analysis of total testosterone and its metabolite, dihydrotestosterone (DHT) will be taken according to the Schedule of Activities given in the protocol.

The following PK parameters will be calculated for total testosterone (baseline corrected and uncorrected) and its metabolite, DHT (if possible) from the concentration-time data using standard noncompartmental methods:

Table 2. Noncompartmental PK Parameters

PK Parameter	Analysis Scale	Total Testosterone	DHT
AUC_{inf}*	ln	A, D	D
AUC_{last}	ln	A, D	D
C_{max}	ln	A, D	D
CCI	[redacted]	[redacted]	[redacted]
$t_{1/2}$*	R	D	D

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

Baseline corrected total testosterone will be determined by utilizing the mean of the 4 predose measurements (-1.0, -0.5, -0.25 and 0 hours) taken within each period.

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 treatment 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

Bioequivalence of PK parameters will be determined by constructing 90% confidence intervals around the estimated difference between the Test and Reference treatments using a mixed effects model based on natural log transformed data. The mixed effects model will be implemented using SAS Proc Mixed, with REML estimation method and Kenward-Roger degrees of freedom algorithm.

8.2. Statistical Analyses

Part 1

Natural log transformed AUC_{last}, AUC_{inf} (if data permit) and C_{max} of total testosterone (baseline corrected [mean of the 4 predose measurements] and uncorrected) will be analyzed separately using a mixed effect model with sequence, period and treatment as fixed effects and subject within sequence as a random effect. Estimates of the adjusted mean differences (Test – Reference) and corresponding 90% confidence intervals will be obtained from the model. The adjusted mean differences and 90% confidence intervals for the differences will be exponentiated to provide estimates of the ratio of adjusted geometric means (Test/Reference) and 90% confidence intervals for the ratios.

The PK parameters for total testosterone (baseline corrected and uncorrected) of AUC_{inf}, AUC_{last}, percent of AUC_{inf} (if data permit) obtained by forward extrapolation ($AUC_{\%extrap}$), C_{max}, CCI *and terminal elimination half-life ($t_{½}$) (if data permit) will be summarized descriptively by analyte and treatment. The PK parameters for DHT of C_{max},* CCI *AUC_{inf}, AUC_{last}, (if data permits), and $t_{½}$ (if data permits) will also be summarized descriptively by analyte and treatment. For AUC_{inf}, AUC_{last} and C_{max}, individual subject parameters will be plotted by analyte and treatment. Concentrations will be listed by analyte and summarized descriptively by PK sampling time and treatment. Individual subject, mean and median profiles of the concentration-time data will be plotted by analyte against treatment (both linear and semi-log scales). For summary statistics and summary (mean and median) 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.*

Part 2

Bioequivalence of the 2 treatments will be assessed in Part 2 and concluded if the 90% confidence intervals for the ratio of adjusted geometric means for AUC_{inf}, AUC_{last}, and C_{max} fall wholly within (80%, 125%). However, the bounds of the acceptance interval may widen based on scaled bioequivalence methodology (See steps below to apply reference scaled average bioequivalence).

Natural log transformed AUC_{last}, AUC_{inf} (if data permit) and C_{max} of total testosterone (baseline corrected [mean of the 4 predose measurements] and uncorrected) will be analyzed separately using a mixed effect model with sequence, period and treatment as fixed effects and subject within sequence as a random effect. Estimates of the adjusted mean differences (Test – Reference) and corresponding 90% confidence intervals will be obtained from the model. The adjusted mean differences and 90% confidence intervals for the differences will be exponentiated to provide estimates of the ratio of adjusted geometric means (Test/Reference) and 90% confidence intervals for the ratios.

Residuals from the model 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.

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

Method for Statistical Analysis Using the Reference-Scaled Average Bioequivalence Approach

Step 1. Determine s_{WR}, the within-subject standard deviation (SD) of the reference product, for the pharmacokinetic (PK) parameters AUC_{inf} (if data permit, otherwise AUC_{last}) and C_{max}.

a. If s_{WR} <0.294, use the two one-sided tests procedure described above to determine bioequivalence (BE) for the individual PK parameter(s)

b. If s_{WR} ≥0.294, use the reference-scaled procedure to determine BE for the individual PK parameter(s)

Calculation for s_{WR} can be conducted as follows (SAS code available in 0):

$$s_{WR}^2 = \frac{\sum_{i=1}^{m}\sum_{j=1}^{n_i}(D_{ij} - \bar{D}_{i\cdot})^2}{2(n-3)}$$

Where:

i = sequence number

j = subjects within each sequence

Dij = Rij1 – Rij2 (where 1 and 2 represent replicate reference treatments)

$$\bar{D}_{i\cdot} = \frac{\sum_{j=1}^{n_i} D_{ij}}{n_i}$$

$$n = \sum_{i=1}^{m} n_i$$

Note: AUCinf (if data permit, otherwise AUClast) and Cmax may have different s_{WR} values. The reference-scaled procedure will only be used for the specific PK parameter(s) that has a s_{WR} ≥0.294. The two one-sided tests procedure will be used for PK parameters with s_{WR} <0.294.

Continue with Steps 2 and 3 for PK parameters that have s_{WR} ≥0.294.

Step 2. Determine the 95% upper confidence bound for:

$$(\bar{Y}_T - \bar{Y}_R)^2 - \left(\frac{\ln(1.25)}{0.25}\right)^2 s_{WR}^2$$

Where:

$\bar{Y}_T$ and $\bar{Y}_R$ are the means of the natural log transformed PK endpoint (AUCinf and/or Cmax) obtained from the study for the test and reference products, respectively.

See SAS code in the Appendix 1 for procedure to calculate the 95% upper bound.

Step 3. For the test treatment to be bioequivalent to the reference treatment, both of the following conditions must be satisfied for each PK parameter tested:

a. The 95% upper confidence bound for $(\bar{Y}_T - \bar{Y}_R)^2 - \left(\frac{\ln(1.25)}{0.25}\right)^2 s_{WR}^2$ must be ≤0.

AND

b. The point estimate of the Test/Reference geometric mean ratio must fall within [0.80, 1.25].

The PK parameters for total testosterone (baseline corrected and uncorrected) of AUC_{inf} (if data permit), AUC_{last}, C_{max}, CCI *and terminal elimination half-life ($t_{½}$) (if data permit) will be summarized descriptively by analyte and treatment. The PK parameters for DHT of C_{max},* CCI *AUC_{inf}, AUC_{last}, (if data permits), and $t_{½}$ (if data permits) will also be summarized descriptively by analyte and treatment.*

Table 3. PK Parameters to be Summarized Descriptively by Analyte and Treatment

Parameter	Summary Statistics
AUC_{inf}* AUC_{last} C_{max}	N, arithmetic mean, median, cv%, standard deviation, minimum, maximum, geometric mean and geometric cv%.
CCI	[redacted]
$t_{1/2}$*	N, arithmetic mean, median, cv%, standard deviation, minimum, maximum.

* If data permits

For AUC_{inf}, AUC_{last} and C_{max} a listing of the individual subject ratios (Test/Reference) will be provided. Box and whisker plots for individual subject parameters (AUC_{inf}, AUC_{last} and C_{max}) will be presented by analyte and treatment and overlaid with geometric means.

Supporting data from the estimation of t½ and AUC_{inf} will be listed by treatment and analyte: terminal phase rate constant (k_{el}); goodness of fit statistic from the log-linear regression (r^2); the percent of AUC_{inf} CCI [redacted] 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.

Separate presentations for total testosterone (baseline corrected and uncorrected) and DHT concentrations will include:

- A listing of all concentrations sorted by subject ID, period 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 treatment 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 treatment (all treatments on the same plot per scale, based on the summary of concentrations by treatment and time postdose).

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

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

- Individual concentration time plots by subject (on both linear and semi-log scales) against actual time postdose [there will be separate plots for each subject (containing all treatments) 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

A set of summary tables split by cohort (Part) and treatment will be produced to evaluate any potential risk associated with the safety and toleration of administering study treatments.

8.3.1. Treatment and Disposition of Subjects

Subject evaluation groups will show end of study subject disposition. Frequency counts will be supplied for subject discontinuation(s) by treatment.

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 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 treatment.

Data will be reported in accordance with the sponsor reporting standards. Data NULL Tables or Listings will not be produced if there are no records in the database.

8.3.4. Adverse Events

Adverse events will be reported in accordance with the sponsor reporting standards by treatment.

CCI [redacted]

CCI

8.3.8. Other Safety Data

None.

8.3.9. Concomitant Treatments

All concomitant medication(s) as well as non-drug treatment(s) will be provided in the listings. Data NULL Tables or Listings will not be produced if there are no records in the database.

8.3.10. Screening and Other Special Purpose Data

Prior medication(s) and non-drug treatment(s), inclusion/exclusion criteria, medical history, physical examination, urine drug screen, alcohol blood test or alcohol breath test, PSA test and rectal examination, HIV, HepBsAg, HepBcAb, and HCVAb testing will be obtained at Screening.

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

Demography data (including height and weight) will be summarized and listed in accordance with the sponsor reporting standards.

Primary diagnosis will be listed in accordance with the sponsor reporting standards.

9. REFERENCES

1. "Implementation of a Reference-Scaled Average Bioequivalence Approach for Highly Variable Generic Drug Products by the US Food and Drug Administration," Barbara M. Davit, Mei-Ling Chen, Dale P. Conner, Sam H. Haidar, Stephanie Kim, Christina H. Lee, Robert A. Lionberger, Fairouz T. Makhlouf, Patrick E. Nwakama, Devvrat T. Patel, Donald J. Schuirmann, and Lawrence X. Yu, *The AAPS Journal*, Vol. 14, No. 4, December 2012; 915-924.

2. "FDA Draft Guidance for Industry, bioequivalence recommendations for progesterone oral capsules," US Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research, Silver Spring. 2011. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM209294.pdf.

10. APPENDICES

Appendix 1. SAS CODE FOR ANALYSES

An example of the PROC MIXED code is provided below:

Part 1:

```
proc mixed data=tab.pk;
        class seq period trt subject;
        model l&var=seq period trt/ ddfm=KR;
        random subject(seq) /subject=subject(seq);
        lsmeans trt;
        estimate 'Test vs Reference' trt 1  -1  /cl alpha=0.1;
        ods 'Estimates' out=est&var;
        ods 'lsmeans' out=ls&var;
        ods 'covparms' out=cov&var;
        ods 'tests3' out=tst&var;
run;
/* Letter assignments for treatments (trt) within the estimate statement above are as follows;
A = New Formulation testosterone cypionate solution for injection 200 mg/mL (Test);
B = Commercial testosterone cypionate solution for injection 200 mg/mL (Reference)  */;
```

Part 2:

```
proc mixed data=tab.pk;
        class seq period trt subject;
        model l&var=seq period trt/ ddfm=satterth;
        random trt / type=fa0(2) sub=subject G;
```

```
        repeated / grp=trt sub=subject;
        lsmeans trt;
        estimate 'Test vs Reference' trt 1  -1  /cl alpha=0.1;
        ods 'Estimates' out=est&var;
        ods 'lsmeans' out=ls&var;
        ods 'covparms' out=cov&var;
        ods 'tests3' out=tst&var;
run;
/* Letter assignments for treatments (trt) within the estimate statement above are as follows;
A = New Formulation testosterone cypionate solution for injection 200 mg/mL (Test);
B = Commercial testosterone cypionate solution for injection 200 mg/mL (Reference)  */;
```

SAS CODE FOR REFERENCE SCALED AVERAGE BIOEQUIVALENCE

```
* dataset containing TEST observations:
data test; set tab.pk;
  if trt=”T”;
  latt=l&var;
run;

* dataset containing REFERENCE 1 observations:
data ref1; set ref;
  if (seq=1 and period=2) or (seq=2 and period=1) or (seq=3 and period=1);
  lat1r=l&var;
run;

* dataset containing REFERENCE 2 observations:
data ref2; set ref;
  if (seq=1 and period=3) or (seq=2 and period=3) or (seq=3 and period=2);
  lat1r=l&var;
run;

* determine Iij and Dij:
data scavbe; merge test ref1 ref2;
```

```
  by seq subject;
  ilat=latt-(0.5*(lat1r+lat2r));
  dlat=lat1r-lat2r;
run;

* intermediate analysis - ilat:
proc glm data=scavbe;
  class seq;
  model ilat=seq/clparm alpha=0.1;
  estimate 'average' intercept 1 seq 0.33333333 0.33333333 0.33333333;
  ods output overallanova=iglm1;
  ods output estimates=iglm2;
  ods output nobs=iglm3;
run;

data iglm2; set iglm2;
  pointest=exp(estimate);
  x=estimate**2-stderr**2;
  boundx=(max((abs(LowerCL)),(abs(UpperCL))))**2;
run;

* Intermediate analysis – dlat
proc glm data=scavbe;
  class seq;
  model dlat=seq;
  ods output overallanova=dglm1;
  ods output nobs=dglm3;
run;

data dglm1; set dglm1;
  dfd=df;
  s2wr=ms/2;
run;

* from above parameters, calculate final 95% upper confidence bound:
data glms; merge iglm2 dglm1;
  theta=((log(1.25))/0.25)**2;
  y=-theta*s2wr;
  boundy=y*dfd/cinv(0.95,dfd);
  swr=sqrt(s2wr);
  critbound=(x+y)+sqrt(((boundx-x)**2)+((boundy-y)**2));
run;
```