# Protocol *A0281006*

***A 2 COHORT, SINGLE DOSE, OPEN-LABEL, RANDOMIZED, PIVOTAL BIOEQUIVALENCE STUDY TO QUALIFY MANUFACTURING SITE TRANSFER FROM BARCELONETA TO ASCOLI FOR PRAZOSIN HYDROCHLORIDE CAPSULES IN HEALTHY ADULT PARTICIPANTS UNDER FASTED CONDITIONS***

# Statistical Analysis Plan (SAP)

**Version:** 1.0

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## Revision History

| Version | Date | Author(s) | Summary of Changes/Comments |
|---|---|---|---|
| 1.0 | July 5, 2021 | PPD | Not Applicable |

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

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## APPENDICES

## 1. AMENDMENTS FROM PREVIOUS VERSION(S)

None.

## 2. INTRODUCTION

CCI [redacted]

### 2.1. Study Design

*This will be a 2 Cohort, open-label, randomized, single dose study in healthy adult male and/or female participants. Cohort 1 will be crossover with 3 treatments, 3 periods, 6 sequences. Cohort 2 will be crossover with 2 treatments, 2 periods, 2 sequences. Approximately 36 participants will be enrolled in each of Cohort 1 and Cohort 2. Participants enrolled in Cohort 1 will not be eligible for Cohort 2 and vice versa. Dropouts for non-safety reasons may be replaced at the discretion of the sponsor and investigator. Participants in Cohort 1 will be assigned to 1 of the 6 sequences according to a computer-generated randomization schedule (see Table 1). Participants in Cohort 2 will be assigned to 1 of the 2 sequences according to a computer-generated randomization schedule (see Table 2).*

**Table 1. Study Schematic: Sequences for Cohort 1**

| ***Sequence*** | ***Period 1*** | ***Washout Period*** | ***Period 2*** | ***Washout Period*** | ***Period 3*** |
|---|---|---|---|---|---|
| *1 (N = 6)* | *A* | At least 7 days | *B* | At least 7 days | *C* |
| *2 (N = 6)* | *B* | | *C* | | *A* |
| *3 (N = 6)* | *C* | | *A* | | *B* |
| *4 (N = 6)* | *A* | | *C* | | *B* |
| *5 (N = 6)* | *B* | | *A* | | *C* |
| *6 (N = 6)* | *C* | | *B* | | *A* |

*Treatment A: Prazosin HCL 1 x 2 mg capsule manufactured at the current site (Barceloneta) under fasting conditions (Reference).*

*Treatment B: Prazosin HCl 1 x 2 mg capsule manufactured at the proposed site (Ascoli) under fasting conditions (Test 1).*

*Treatment C: Prazosin HCl 2 x 1 mg capsule manufactured at the proposed site (Ascoli) under fasting conditions (Test 2).*

**Table 2. Study Schematic: Sequences for Cohort 2**

| ***Sequence*** | ***Period 1*** | ***Washout Period*** | ***Period 2*** |
|---|---|---|---|
| *1 (N = 18)* | *D* | At least 7 days | *E* |
| *2 (N = 18)* | *E* | | *D* |

*Treatment D: Prazosin HCl 1 x 5 mg capsule manufactured at the current site (Barceloneta) under fasting conditions (Reference).*
*Treatment E: Prazosin HCl 1 x 5 mg capsule manufactured at the proposed site (Ascoli) under fasting conditions (Test).*

*On Day 1 of each period, participants will receive a single dose of investigational product as per randomization schedule. Study treatments will be administered with approximately 240 mL of ambient temperature water under fasting conditions (overnight fast and no food until 4 hours after dosing). Water will be allowed without restriction until 1 hour prior to dosing and may be consumed without restriction beginning 1 hour after dosing.*

*Blood samples for the analysis of prazosin in plasma will be obtained predose (immediately prior to dosing) and postdose as outlined in Schedule of Activities (Study Protocol' SoA) table. Tolerability and safety will be assessed for all treatments by monitoring AEs.*

## 2.2. Study Objectives

Primary:

- *To demonstrate bioequivalence between prazosin HCL 1 and 2 mg capsules manufactured at the proposed site (Ascoli) versus prazosin HCl 2 mg capsules manufactured at the current site (Barceloneta) under fasting conditions in healthy adult participants.*

- *To demonstrate bioequivalence between prazosin HCl 5 mg capsules manufactured at the proposed site (Ascoli) versus prazosin HCl 5 mg capsules manufactured at the current site (Barceloneta) under fasting conditions in healthy adult participants.*

Secondary:

- *To evaluate the safety and tolerability of prazosin HCl capsules.*

# 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 PK/PD modeling, and/or supporting clinical development.*

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

### 4.1.1. Bioequivalence Hypotheses

*The alternative hypothesis of bioequivalence ($H_1$: $\theta_L <= \mu_T - \mu_R <= \theta_U$), and the null hypothesis of inequivalence ($H_o$: $\mu_T - \mu_R < \theta_L$ or $\mu_T - \mu_R > \theta_U$) can be expressed as the following two separate one-sided hypotheses:*

$H_{OA}$: $\mu_T - \mu_R < \theta_L$

$H_{1A}$: $\mu_T - \mu_R >= \theta_L$

$H_{OB}$: $\mu_T - \mu_R > \theta_U$

$H_{1B}$: $\mu_T - \mu_R <= \theta_U$

*where $\mu_T$ and $\mu_R$ represent the average bioavailability on a log scale for the Test and Reference products, respectively and $[\theta_L, \theta_U]$ defines the bioequivalence range.*

*Bioequivalence of the Test treatment to Reference treatment will be concluded if the 90% confidence intervals for the ratios of adjusted geometric means for prazosin $AUC_{last}$ and $C_{max}$ fall entirely within the acceptance region of (80%, 125%).*

## 4.2. Statistical Decision Rules

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

### 4.2.1. Average Bioequivalence Decision Rules

The two one-sided hypotheses are tested at the $\alpha$= 0.05 levels of significance for log-transformed $AUC_{last}$ 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 $AUC_{last}$ and $C_{max}$ fall entirely within (80%, 125%).

## 5. ANALYSIS SETS

### 5.1. Enrolled/Randomly Assigned to Study Intervention

*Participants will be randomized into the study provided they have satisfied all participant eligibility criteria.*

### 5.2. Pharmacokinetic (PK) Analysis Set

#### 5.2.1. Concentration Analysis Set

*All participants randomized and treated who have at least 1 concentration in at least 1 treatment period.*

#### 5.2.2. Parameter Analysis Set

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

### 5.3. Pharmacodynamic Analysis Set

None.

### 5.4. Safety Analysis Set

*All participants randomly assigned to study intervention and who take at least 1 dose of investigational product.*

### 5.5. Other Analysis Sets

None.

### 5.6. 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 received for all safety, PK and pharmacodynamic analyses, where applicable.

### 5.7. 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.

#### 5.7.1. Deviations Assessed Prior to Randomization

At Screening, the investigator will assess participants against the inclusion and exclusion criteria as set out in the protocol.

#### 5.7.2. 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

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

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

- *adverse events,*
- *laboratory data.*

### 6.3. Other Endpoints

#### 6.3.1. PK Endpoints

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

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

**Table 3. Noncompartmental PK Parameters**

| PK Parameter | Analysis Scale | Prazosin |
|---|---|---|
| $AUC_{inf}$* | ln | A, D |
| $AUC_{last}$ | ln | A, D |
| $C_{max}$ | ln | A, D |
| $T_{max}$ | R | D |
| $t_{1/2}$* | 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 (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 (ie, not calculated). Note that NC values will not be generated beyond the day that a participant discontinues.

In summary tables, statistics will be calculated by setting NC values to missing; and statistics will be presented for a particular 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 participant has a known biased estimate of a PK parameter (for example due to an unexpected event that might occur 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.

If an individual participant has a predose concentration ≤5 percent of the $C_{max}$ value, then that participant's data can be included in all pharmacokinetic measurements and calculations without any adjustments. If the predose value is >5 percent of $C_{max}$, the PK parameters for that period will be excluded for that participant from all bioequivalence evaluations.

## 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

*Pharmacokinetic and statistical analysis will be performed for prazosin. Data from the 2 Cohorts will be analyzed separately.*

Cohort 1:

*Natural log transformed PK parameters ($AUC_{inf}$ (if data permit), $AUC_{last}$, and $C_{max}$) will be analyzed using a mixed effect model with sequence, period and treatment as fixed effects and participant within sequence as a random effect. Estimates of the adjusted mean differences (Test-Reference) and the corresponding 90% confidence intervals will be obtained from the model. The adjusted mean differences and the 90% confidence intervals for the differences will be exponentiated to provide estimates of the ratio of adjusted geometric means (Test/Reference) and the 90% confidence intervals for the ratios.*

*For primary objective, bioequivalence of the Test treatments (Treatment B and Treatment C) relative to Reference treatment (Treatment A) will be concluded if the 90% confidence intervals for the ratio of adjusted geometric means of Test treatments (Treatment B and Treatment C) relative to Reference treatment (Treatment A) for $AUC_{last}$ and $C_{max}$ fall wholly within (80%, 125%).*

Cohort 2:

*Natural log transformed PK parameters ($AUC_{inf}$ (if data permit), $AUC_{last}$, and $C_{max}$) will be analyzed using a mixed effect model with sequence, period and treatment as fixed effects and participant within sequence as a random effect. Estimates of the adjusted mean differences (Test-Reference) and the corresponding 90% confidence intervals will be obtained from the model. The adjusted mean differences and the 90% confidence intervals for the differences will be exponentiated to provide estimates of the ratio of adjusted geometric means (Test/Reference) and the 90% confidence intervals for the ratios.*

*For primary objective, bioequivalence of the Test treatment (Treatment E) relative to Reference treatment (Treatment D) will be concluded if the 90% confidence intervals (CI) for the ratio of adjusted geometric means of Treatment E (5 mg capsule, Ascoli) relative to Treatment D (5 mg capsule, Barceloneta) for $AUC_{last}$ and $C_{max}$, fall wholly within (80%, 125%).*

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.

*The PK parameters $AUC_{last}$, $AUC_{inf}$, $C_{max}$, $T_{max}$, and $t_{½}$ will be summarized descriptively by treatment.*

**Table 4. PK Parameters to be Summarized Descriptively by Treatment**

| Parameter | Summary Statistics |
|---|---|
| $AUC_{inf}$, $AUC_{last}$, $C_{max}$ | N, arithmetic mean, median, cv%, standard deviation, minimum, maximum, geometric mean and geometric cv%. |
| $T_{max}$ | N, median, minimum, maximum. |
| $t_{1/2}$ | N, arithmetic mean, median, cv%, standard deviation, minimum, maximum. |

Box and whisker plots for individual participant parameters ($AUC_{inf}$, $AUC_{last}$ and $C_{max}$) will be presented by treatment and overlaid with geometric means.

Supporting data from the estimation of $t_{½}$ and $AUC_{inf}$ will be listed by treatment: 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 prazosin concentrations will include:

- A listing of all concentrations sorted by participant 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 concentration 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 participant (on both linear and semi-log scales) against actual time postdose [there will be separate plots for each participant (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 participant plots by time, the actual PK sampling time will be used.

### 8.3. Safety Analysis

A set of summary tables split by treatment will be produced to evaluate any potential risk associated with the safety and toleration of administering prazosin.

#### 8.3.1. Treatment and Disposition of Participants

Participant evaluation groups will show treated and not-treated study participant disposition and will show which participants were analyzed for safety (adverse events and laboratory data). Frequency counts will be supplied for participant discontinuation(s) by treatment.

### 8.3.2. Demographic and Clinical Examination Data

A breakdown 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 Participants' in accordance with the sponsor reporting standards.

### 8.3.3. Discontinuation(s)

Participant discontinuations and temporary discontinuations due to adverse events will be detailed and summarized by treatment.

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 Pfizer reporting standards by treatment.

### 8.3.5. Laboratory Data

Laboratory data will be listed and assessed against the criteria specified in the sponsor reporting standards.

The baseline measurement for a given period is the planned predose measurement at Day -1 of that period.

### 8.3.6. Vital Signs Data

Vital Signs data will be databased and available upon request.

### 8.3.7. ECG Data

ECG data will be databased and available upon request.

### 8.3.8. Other Safety Data

COVID data will be listed.

### 8.3.9. Concomitant Treatments

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

### 8.3.10. Screening and Other Special Purpose Data

Screening data will available upon request.

## 9. REFERENCES

None.

# APPENDICES

## Appendix 1. SAS CODE FOR BE ANALYSIS

An example of the PROC MIXED code is provided below:

Cohort 1:

Comparison of Treatment B Prazosin HCl 1 x 2 mg capsule manufactured at the proposed site (Ascoli) and Treatment C Prazosin HCl 2 x 1 mg capsule manufactured at the proposed site (Ascoli) versus Treatment A Prazosin HCl 1 x 2 mg capsule manufactured at the current site (Barceloneta)

```
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 ‘Treatment B vs Treatment A ' trt   -1  1  0  /cl alpha=0.1;
        estimate ‘Treatment C vs Treatment A ' trt   -1  0  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;

Treatment A: Prazosin HCl 1 x 2 mg capsule manufactured at the current site (Barceloneta) under fasting conditions (Reference).

Treatment B: Prazosin HCl 1 x 2 mg capsule manufactured at the proposed site (Ascoli) under fasting conditions (Test 1).

Treatment C: Prazosin HCl 2 x 1 mg capsule manufactured at the proposed site (Ascoli) under fasting conditions (Test 2).*/
```

Cohort 2:

Comparison of Treatment E Prazosin HCl 1 x 5 mg capsule manufactured at the proposed site (Ascoli) versus Treatment D Prazosin HCl 1 x 5 mg capsule manufactured at the current site (Barceloneta)

```
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 'Treatment E vs Treatment D ' 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;

Treatment D: Prazosin HCl 1 x 5 mg capsule manufactured at the current site (Barceloneta) under fasting conditions (Reference).

Treatment E: Prazosin HCl 1 x 5 mg capsule manufactured at the proposed site (Ascoli) under fasting conditions (Test).

.*/