STATISTICAL ANALYSIS PLAN

Bigg Pharmaceutical Company
1600 Huron Parkway
Ann Arbor, MI 48105

A Multi-center Randomized, Double-blind, Placebo-controlled Study of BP3304 in Patients with Hypertension

Clinical Study Protocol No. BP3304-002

Prepared by
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SIGNATURE PAGE

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Clinical Study Protocol No. BP3304-002

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

β	Beta
µg	Microgram
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine transaminase
ANCOVA	Analysis of covariance
AST	Aspartate transaminase
BP	Blood pressure
BUN	Blood urea nitrogen
CNS	Central nervous system
CRF	Case report form
CS	Clinically significant
CV	Cardiovascular
DBP	Diastolic blood pressure
DSMB	Drug safety monitoring board
ECG	Electrocardiogram
eCRF	Electronic case report form
FDA	Food and Drug Administration
GCP	Good clinical practice
GGT	Gamma-glutamyl transferase
GLP	Good laboratory practice
H or hr	Hour
Hb	Hemoglobin
HCT	Hematocrit
HDL	High density lipoprotein
HR	Heart rate
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IRB/EC	Institutional review board/Ethics committee
iv	Intravenous

kg	Kilogram
LDL	Low density lipoprotein
m^2	Square meters
MCH	Mean cell hemoglobin
MCHC	Mean cell hemoglobin concentration
MCV	Mean cell volume
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
min	Minute
MITT	Modified intent to treat
mL	Milliliter
NCS	Not clinically significant
NSAID	Non-steroidal anti-inflammatory drug
^oC	Degrees Celsius
PI	Principal Investigator
PK	Pharmacokinetic
RBC	Red blood cell
SAE	Serious adverse event
SAP	Statistical analysis plan
SBP	Systolic blood pressure
sc	Subcutaneous
SD	Standard deviation
VLDL	Very low density lipoprotein
WBC	White blood cell

1. INTRODUCTION

This proposed 6-month Phase III study will evaluate the safety and effects of BP3304 as a treatment for hypertension. More specific details regarding the study design can be found in Section 1.2 of this statistical analysis plan (SAP).

This SAP describes the planned data summaries and statistical analyses to be performed for the Phase III trial conducted under Protocol BP3304-002 dated 29 August 2009. It is intended to supplement the study protocol, which contains details regarding the objectives and design of the study. Any deviations from this analysis plan will be described in the clinical study report (CSR).

1.1 Study Objectives

The objective of this clinical trial is to evaluate the efficacy and safety of BP3304 compared to placebo at a dosage of 100 mg once daily in patients with hypertension. Safety and efficacy will be evaluated by assessing the following:

- Change from baseline to Month 6 in systolic and diastolic blood pressure
- Time until the first diastolic blood pressure $\leq$ 90 mmHg is achieved
- Extent of exposure
- Incidence of adverse events (AEs) and serious adverse events (SAEs)
- Concomitant medication use
- Laboratory safety tests
- Vital signs, ECG, physical examination, weight

The secondary objectives of the trial are to (1) evaluate the efficacy of BP3304 as a treatment for hypertension in patients over 65 years old, and (2) evaluate the efficacy of BP3304 as a treatment for hypertension in patients diagnosed more than 10 years prior to enrollment in this study.

1.2 Study Design

The protocol will follow a multi-center, double-blind, randomized, placebo-controlled design for the study of BP3304 in patients with hypertension.

The study duration for individual patients will be up to 6 months (24 weeks) and will consist of 3 phases, specifically, a screening/baseline phase (up to 1 week), a Treatment Phase (20 weeks), and a Follow-up Phase (4 weeks).

During the screening/baseline phase, all patients will discontinue any hypertension medications.

The Treatment Phase is 20 weeks long and during this time, patients will self-administer study drug orally once daily.

The Follow-up Phase, during which no study drug will be taken, will start after the last dose of study drug and patients will be followed for an additional 4 weeks (1 month). During the Follow-up Phase, patients will be seen at the clinic at Week 1 and Week 4, and the site will telephone the patient weekly to review AEs and changes to concomitant medications.

1.3 Study Timepoints

The schedule of study events and time points can be found in Table 1.

Table 1: Schedule of Study Events and Time Points

	SCREENING/ BASELINE PHASE[1]		TREATMENT PHASE[2]						FOLLOW-UP PHASE[3]		EARLY TERMINATION[4]
	Visit 1	Visit 2	V3	V4	V5	V6	V7	V8	V9	V10	
PROCEDURES	**Screening (Start up to 28 days before D1)**	**Baseline (Complete within 7 days of D1)**	**Day 1**	**Wk 4 ± 2d**	**Wk 8 ± 2d**	**Wk 12 ± 2d**	**Wk 16 ± 2d**	**Wk 20 ± 2d**	**Wk 21 ± 4d**	**Wk 24 ± 7d**	**ET Visit for W/D < Wk 20**
Informed Consent	X										
Incl/Excl Review	X	X	X								
Demographics	X										
Medical History	X	X	X								
Vital Signs[5]	X	X	X	X	X	X	X	X		X	X
Physical Examination[6]	X	X		X		X				X	X
ECG[7]	X									X	X
Pregnancy Test[8]	X	X	X								X
Clinical Lab Tests[9]	X	X	X	X	X	X	X	X		X	X
Randomization			X								
Study Drug Dosing			X	X	X	X	X	X			
Telephone Contact[10]									X		
AE Review	X	X	X	X	X	X	X	X	X	X	X
Medication Review	X	X	X	X	X	X	X	X	X	X	X

[1] Screening/Baseline can occur up to 28 days before Day 1. For site and patient convenience, Screening assessments may occur on different days during the Screening period. Once all Screening assessments are completed and approved, the Baseline visit can occur. The Baseline visit must occur within 7 days of dosing (Day 1).

[2] The Treatment Phase is 20 weeks long. Visits will be anchored to the Day 1 date (1st dose) so the Week 4 visit will occur 4 weeks ± 2 days of Day 1 and the Week 8 visit will occur 8 weeks ± 2 days of Day 1 etc.

[3] The Follow-up Phase is 1 month long. Visits will be anchored to the Day 1 date. For example, if a patient completes the 20-week Treatment Phase, then the Week 21 Follow-up visit will occur 21 weeks ± 4 days of Day 1, and the Week 24 Follow-up visit will occur 24 weeks ± 7 days of Day 1.

[4] Withdrawals/Early Termination (ET) will be handled differently during different study phases. All efforts will be made to complete the required assessments as close to the time of study drug discontinuation as possible. Patients discontinuing drug before the Week 20 visit will undergo the ET visit and will then enter into the 1-month Follow-up Phase, providing safety assessments only. Follow-up Phase visits will be anchored to the date of the last dose of study drug.

[5] Vital signs will be measured at all visits. During the Treatment Phase, vitals will be measured pre-dose. Blood pressure (BP) and heart rate (HR) will be collected. Vital sign measurements will be determined after patients have been seated quietly for at least 5 minutes. An appropriately sized cuff (cuff bladder encircling at least 80% of the arm) should be used to ensure accuracy of measurements. Sitting measurements should be determined with patients seated in a chair (rather than on an exam table) and with feet on the floor. The arm

used for blood pressure measurements should be supported at heart level.

[6] Complete physical examinations should include a review of all body systems. Height will be assessed at Screening only and weight will be recorded at each physical examination. At the Week 24 visit, weight only will be assessed.

[7] Triplicate ECG tracings will be obtained at Screening only. At all post-dose time points, a single ECG tracing will be obtained.

[8] Serum pregnancy tests, for females of childbearing potential, will be performed at all indicated visits, except on Day 1 (Visit 3) when a urine pregnancy test will be performed prior to the 1st dose of study drug.

[9] Patients will fast for a minimum of 8 hours prior to clinical laboratory tests.

[10] To ensure that patient safety is well monitored throughout the entire study, the Study Coordinators will telephone patients to review AEs, concomitant medications, any lifestyle changes and also answer any questions that patients may have. Telephone contact will occur in the Follow-up Phase. During the Follow-up Phase, patients will be seen at the site at Week 24. The Study Coordinator will telephone patients at Week 21 to review safety.

2. STUDY POPULATIONS

Data from this trial will be summarized and analyzed for 3 analysis populations, namely the safety population, the modified intent to treat population, and the Completers population, defined as follows. Efficacy analyses will be performed on both the MITT and Completers populations.

Safety Population: This analysis population will include all patients who are randomized and receive at least one dose of study medication. Safety analyses will be based on the safety population.

Modified Intent to Treat (MITT) Population: This analysis population will include all patients in the safety population who have a baseline diastolic blood pressure value and at least one post-baseline diastolic blood pressure value. Efficacy analysis will be based on the MITT population.

Per Protocol Population: This analysis population will include all patients in the MITT population who took at least 80% of intended treatment doses (or 112 doses) with no major protocol deviations. Major protocol deviations will be identified by the Medical Monitor prior to database lock and unblinding.

3. DEFINITIONS AND DERIVED VARIABLES

Study Day: Day 1 will be defined as the first date on which study drug was administered. Positive study days will be counted forward from Day 1. Day -1 will be the date immediately preceding Day 1, and negative study days will be counted backward from Day -1.

Baseline: For all other parameters, the baseline measurement will be the pre-dose value collected on Day 1 or if not available, then the last value collected before Day 1.

Change: Change from baseline at a particular post-baseline time point will be computed as the value at the post-baseline time point minus the baseline value.

Duration of Exposure: Duration of exposure (weeks) will be computed as the date of the last dose of study drug minus the date of the first dose of study drug, plus 1 day (that is, the study day associated with the date of the last dose of study drug) divided by 7 days per week.

Age: Age in years will be computed as the integer value of the date of informed consent minus the date of birth, divided by 365.25 days per year.

Body Mass Index: Body mass index in kg/m^2 will be computed as weight in kilograms divided by height, in meters, squared.

Conversion Factors: If height is recorded in inches, it will be converted to centimeters using the conversion factor 1 inch = 2.54 centimeters. If weight is recorded in pounds, it will be converted to kilograms using the conversion factor 1 pound = 0.454 kilograms.

Visit Windows: Measurements will be associated with a visit for summarization according to the study day associated with the date on which the information was collected. Target dates and the acceptable range of study days for each visit are presented in Table 2. If multiple visits occur within a visit window, the visit occurring closest to the target day will be selected for summarization. If there is a tie, the earliest visit will be chosen.

Table 2: Visit Windows for Treatment Phase

Visit	Target Day	Acceptable Range of Study Days
Treatment Phase		
Day 1	1	≤ 1
Week 4	28	[26, 30]
Week 8	56	[54, 58]
Week 12	84	[82, 86]
Week 16	112	[110, 114]
Week 20	140	[138, 142]
Follow-up Phase		
Week 24	168	[161, 175]

4. EFFICACY PARAMETERS

Efficacy will be assessed by evaluating the following endpoints.

- The change in diastolic blood pressure from baseline to Weeks 4, 8, 12, 16 and 20 of the Treatment Phase, Week 24 of the Follow-up Phase, and end of study. Diastolic blood pressure data will be obtained from the vital signs dataset.
- The change in systolic blood pressure from baseline to Weeks 4, 8, 12, 16 and 20 of the Treatment Phase, Week 24 of the Follow-up Phase, and end of study. Systolic blood pressure data will be obtained from the vital signs dataset.
- Time in days until the first diastolic blood pressure ≤ 90 mmHg is achieved.
- Proportion of patients achieving diastolic blood pressure ≤ 90 mmHg at Week 20 of Treatment and at Week 24 of Follow-up.
- The change in diastolic blood pressure from baseline to Weeks 4, 8, 12, 16 and 20 of the Treatment Phase, Week 24 of the Follow-up Phase, and end of study in patients over 65 years old.
- The change in diastolic blood pressure from baseline to Weeks 4, 8, 12, 16 and 20 of the Treatment Phase, Week 24 of the Follow-up Phase, and end of study in patients diagnosed with hypertension more than 10 years prior to enrollment in the study.

5. SAFETY PARAMETERS

Safety and tolerability will be assessed by evaluating the following endpoints.

- Extent of exposure
- Incidence of adverse events
- Adverse events reported by ≥ 5% of patients
- Incidence of deaths and serious adverse events
- Laboratory safety tests (hematology, biochemistry, and urinalysis)
- Vital signs
- ECG
- Physical examination, including weight
- Concomitant medications

6. STATISTICAL METHODOLOGY

6.1 Statistical and Analytical Issues

6.1.1 Data Included in Tables and Listings

Data for patients who entered the study but were not randomized (i.e. screen failures) will be included only in the Informed Consent and Subject Disposition Listings. No other data from these patients will be reported. All data from patients randomized in the study will be presented and summarized as applicable.

6.1.2 Statistical Methods

All summarization and listing of data will be performed using SAS Version 8 or higher [1]. Continuous variables will be summarized using non-missing counts (N), mean, standard deviation (SD), median, minimum, and maximum. Categorical variables will be summarized as counts and percentages of patients with non-missing data in particular analysis populations. All data will be summarized by treatment group and cases in which data will be summarized overall will be specified in Sections 6.2 through 6.4.5.

Summaries and analyses will be performed for the efficacy parameters by treatment group.

6.1.3 Handling of Dropouts and Missing Data

Data will be summarized as observed with no imputation for missing values, with the exception that end of study summarization of data will employ a last observation carried forward approach.

6.1.4 Pooling of Investigator Sites

Due to the small sample size relative to the large number of sites, analysis by site will not be conducted and, therefore, pooling of sites will not be performed.

6.1.5 Determination of Sample Size

The primary objective of the current study is to evaluate the efficacy of BP3304 as a treatment for hypertension. The sample size for this study is related to the change from baseline in hypertension observed in a previous study using twice daily regimens of BP3304 in patients with hypertension. Considering a reduction of 20% with standard deviation of 2.8, it was determined that a sample size of approximately 40 patients per treatment group would be required to demonstrate efficacy with a single dose daily compared to placebo in the BP3304 group. A sample size of 60 patients per group should be adequate to fulfill the primary objective, which is to show a statistically significant reduction for change from baseline in diastolic blood pressure at the .05 level of significance with 80% power, and should be sufficient to handle an assumed 20% drop-out rate.

6.2 Patient Characteristics

6.2.1 Patient Disposition and Unblinding

Patient disposition and unblinding will be summarized overall and by site for all enrolled patients for 2 study phases, specifically, the Treatment Phase, and the Follow-up Phase. Unblinding will not be summarized by site but will be presented by patient in the data listings.

The number of patients enrolled in total and the percentage of those enrolled patients who withdraw prior to randomization will be summarized overall and by reason for withdrawal (patient had exclusionary laboratory values, patient had non-laboratory safety exclusions, patient was using excluded concomitant medication, and other).

The number of patients randomized will be presented by treatment group and overall for the Treatment Phase. The number and percentage of randomized patients who complete the Treatment Phase, who discontinue the Treatment Phase, and who discontinue the Treatment Phase by reason for discontinuation (administrative reasons by sponsor, adverse event, death, did not meet inclusion criteria, lost to follow-up, non-compliance, protocol deviation, withdrawn by investigator, patient withdrew consent, and other) will be summarized by treatment group and overall.

The number of patients entering the Follow-up Phase will be presented by treatment group and overall. The number and percentage of patients entering the Follow-up Phase, who complete the Follow-up Phase, who discontinue the Follow-up Phase, and who discontinue the Follow-up Phase by reason for discontinuation (administrative reasons by sponsor, adverse event, death, did not meet inclusion criteria, lost to follow-up, non-compliance, protocol deviation, withdrawn by investigator, patient withdrew consent, and other) will be summarized by treatment group and overall. Time on study (weeks) will be presented by treatment group and overall.

6.2.2 Protocol Deviations

Major protocol deviations will be presented by treatment group and overall. The number and percentage of patients with any major deviation and the number and percentage of patients with major deviations by category (inclusion/exclusion, incorrect study drug assignment, prohibited medications, missed visits and other (specify)) will be presented.

6.2.3 Patient Evaluability

The number and percent of randomized patients who are safety evaluable, not safety evaluable MITT evaluable, and not MITT evaluable, Per Protocol evaluable and not Per Protocol evaluable will be summarized by treatment and overall.

6.2.4 Demographics, Baseline Characteristics and Disease History

The following demographics and baseline characteristics will be summarized descriptively for both the safety and MITT populations: age in years (computed as the date of randomization minus the date of birth, plus 1 day, divided by 365.25 days per year, taking the integer portion of the result), gender, ethnicity (Hispanic or Latino, not Hispanic and not Latino), race (White, Black or African American, Asian, American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, Other), height in centimeters, weight in kilograms, body mass index (computed as weight divided by squared height), alcohol history (never consumed, previously consumed, currently consumes), tobacco history (never used, previously used, currently uses), and duration of hypertension in years (computed as the date of randomization minus the date of hypertension diagnosis, plus 1 day, multiplied by 12 months per 365.25 days).

6.2.5 Medical Histories

General Medical History

General medical history will be listed for the safety population, and will not be summarized.

6.2.6 Prior and Concomitant Medication

Medication data will be summarized for the safety population for both treatment groups and overall, presenting medications prior to and after randomization. Each medication will be mapped to a therapeutic class and preferred term using the current version of the WHO Drug Dictionary (Version 8 March 2008 or later)[3]. The number and percentage of patients taking any medication, any medication within therapeutic class, and taking any medication according to preferred term will be summarized by treatment and overall.

Prior/baseline medications and medications at study entry will include all recorded medications taken prior to the date of the first injection of study drug (Day 1). Concomitant Treatment Phase Medications will include all recorded medications which were taken prior to and continue after Day 1 and those that start on or after Day 1 up until the last dose date plus 1 day, inclusive.

Concomitant Follow-up Phase Medications will include all recorded medications which were taken prior to and continue after the last dose day plus 1 and those that start after the last dose day plus 1. If the start date of a medication is incomplete or missing, the medication will be assumed to be a Treatment Phase medication, unless the incomplete start date (month and/or year) or the stop date (complete or incomplete) clearly indicate that the medication started prior to randomization or in the Follow-up Phase.

Prior Medications
A summary of all medications taken prior to dosing by class and preferred term will be presented.

Concomitant Treatment Phase Medications
A summary of all medications by class and preferred term will be presented for all medications taken during the Treatment Phase as defined above.

Follow-up Phase Medications
A summary of all medications by class and preferred term will be presented for all medications taken during the Follow-up Phase as defined above.

6.2.7 Treatment Exposure and Compliance

Exposure to Study Drug

Exposure to study drug in weeks will be computed for each patient as the date of last dose minus the date of first dose, plus 1 day divided by 7 days per week. Exposure to study drug will be summarized descriptively by treatment and overall for both the safety and MITT populations.

Compliance with Study Drug Dosing During the Treatment Phase

Compliance with study drug dosing during the Treatment Phase will be computed for each patient as the exposure to study drug in days minus the number of Treatment Phase days on which study drug was not administered, divided by exposure to study drug in days, multiplied by 100%. Compliance with study drug dosing during the Treatment Phase will be summarized descriptively by treatment and overall for both the safety and MITT populations.

Number of Study Drug Doses Taken

The total number of doses taken will be computed for each patient and will be summarized by treatment and overall for both the safety and MITT populations.

6.3 Efficacy Analysis

The primary objective of this study is to evaluate the efficacy of BP3304 as a treatment for hypertension. Summaries and analyses will be performed for the efficacy parameters by treatment group. Efficacy will be assessed by the following endpoints:

- The change in diastolic blood pressure from baseline to Weeks 4, 8, 12, 16 and 20 of the Treatment Phase, Week 24 of the Follow-up Phase, and end of study. Diastolic blood pressure data will be obtained from the vital signs dataset.
- The change in systolic blood pressure from baseline to Weeks 4, 8, 12, 16 and 20 of the Treatment Phase, Week 24 of the Follow-up Phase, and end of study. Systolic blood pressure data will be obtained from the vital signs dataset.

- Time until the first diastolic blood pressure ≤ 90 mmHg is achieved. Patients who do not achieve diastolic blood pressure ≤ 90 mmHg by Week 24 will be censored at that visit. Patients who discontinue from the study prior to Week 24 for reasons not related to study conduct, or discontinue secondarily to an adverse event, will be censored at the time of discontinuation and treated as randomly censored.
- Proportion of patients achieving diastolic blood pressure ≤ 90 mmHg at Week 20 of Treatment and at Week 24 of Follow-up.
- The change in diastolic blood pressure from baseline to Weeks 4, 8, 12, 16 and 20 of the Treatment Phase, Week 24 of the Follow-up Phase, and end of study in patients over 65 years old.
- The change in diastolic blood pressure from baseline to Weeks 4, 8, 12, 16 and 20 of the Treatment Phase, Week 24 of the Follow-up Phase, and end of study in patients diagnosed with hypertension more than 10 years prior to enrollment in the study.

Summary statistics (including number of patients, mean, SD, minimum and maximum by visit and by treatment group of the raw and change-from-baseline values will be provided for both diastolic and systolic blood pressure. Baseline will be defined as the average of three measurements taken on Day 1 before the first dose of study drug; change will be defined as the post-baseline value minus the baseline value. If there are no measurements taken on Day 1, the value taken at the screening visit will be used as the baseline value.

For change in diastolic and systolic blood pressure from baseline, a last observation carried forward (LOCF) analysis using an analysis of covariance (ANCOVA) model will be performed. The ANCOVA model will have fixed effects for treatment and baseline therapy strata and a covariate for baseline blood pressure.

Time to event endpoints (time to first diastolic blood pressure ≤ 90 mmHg) will be analyzed using Kaplan-Meier (KM) survival methods (SAS PROC LIFETEST) (Collett 2003, Allison 1995). The KM algorithm will be applied to derive the median event time and the 95% confidence interval for the median for each treatment group. A small number of events (if median is non-estimable) would limit the use of the Kaplan-Meier method to provide reliable information. In this case, descriptive statistics (n, mean, median, standard deviation, min, max) will be provided. Differences in the survival distributions between treatment groups will be assessed using 2-sided log-rank, and Wilcoxon tests with alpha set at the 0.05 level of significance acknowledging the differential emphasis each method places upon earlier verses later events. The event time will be considered a censored time for patients who either complete the study or discontinue prior to achieving the defined event of interest.

For the proportion of patients achieving diastolic blood pressure ≤ 90 mmHg at Week 20, a logistic regression analyses will be used with the same covariates as the ANCOVA described above to compare treatment groups. Frequencies and percentages by treatment group will be provided.

6.4 Safety Analysis

6.4.1 Adverse Events

Each verbatim adverse event (AE) term recorded during the study will be mapped to a system organ class and preferred term using the current MedDRA Dictionary (Version 10.0 or later).

Treatment Emergent Adverse Events (TEAEs) will include all recorded AEs which started on or after Day 1 up until the last dose date plus 14 days, inclusive. If the start date of an AE is incomplete or missing, the event will be assumed to be treatment-emergent, unless the incomplete start date (month and/or year) or the stop date (complete or incomplete) clearly indicate that the event started before Day 1.

Relationship of each AE to study drug will be recorded as "Definitely Not", "Probably Not", "Possibly", "Probably," "Definitely." For summarization AEs recorded "Definitely Not" or "Probably Not" will be "Not Related" and AEs recorded as "Possibly", "Probably," or "Definitely" will be "Related". If a relationship is missing for a given event, the event will conservatively be assumed as related for summarization.

The severity of each AE will be classified as mild, moderate, or severe. If the severity of an event is missing, the event will be assumed "severe" for summarization.

AEs will be summarized for the safety population by treatment and overall.

An overview of TEAEs will summarize the number and percentage of patients and the number of events as follows: Any, severe, treatment-related, resulting in study drug discontinuation during the Treatment Phase, treatment-related resulting in study drug discontinuation during the Treatment Phase, any by maximum severity, and any treatment-related by maximum severity, any SAEs, treatment-related SAEs, SAEs resulting in death and treatment-related SAEs resulting in death.

The number and percentage of patients will be summarized for any event and by system organ class and preferred term for the following sets of events. Patients experiencing multiple events at any level of summarization (any event, system organ class, or preferred term) will be counted only once. Patients experiencing multiple events at any level will be counted only once at the maximum severity experienced.

- TEAEs and treatment-related TEAEs
- Severe TEAEs and treatment-related severe TEAEs

- TEAEs reported by ≥ 5% of all BP3304 patients and treatment-related TEAEs reported by ≥ 5% of all BP3304 patients
- TEAEs resulting in study drug discontinuation and treatment-related TEAEs resulting in study drug discontinuation
- SAEs and treatment-related SAEs
- SAEs resulting in death and treatment-related SAEs resulting in death

TEAEs will also be summarized by maximum severity overall and within system organ class and preferred term (the number and percentage of patients).

6.4.2 Laboratory Parameters

Laboratory parameters will be summarized for patients in the safety population. A complete listing of chemistry, hematology, and urinalysis parameters can be found in Protocol Section 7.4.9, and are also outlined in the table and listing shells which accompany this statistical analysis plan. Laboratory parameters are to be collected at screening, baseline, Treatment Phase Weeks 4, 8, 12, 16, and 20, and Follow-up Phase Week 24.

Observed values of continuous chemistry and hematology laboratory parameters at each visit and change from baseline in these parameters at each post-baseline visit will be summarized descriptively by treatment group (N, mean, standard deviation, median, minimum, and maximum). Baseline will be defined as the last value collected before the first dose of study drug; change from baseline will be computed as the value at the post-baseline visit minus the value at baseline.

Laboratory parameters will also be summarized in shift tables by treatment, to determine the number and percentage of patients with measurements classified as normal or abnormal at each post-baseline visit with reference to the same classification at baseline. Chemistry and hematology parameters (which are continuous in nature) will use the classifications of low, normal, and high relative to normal ranges, whereas appropriate categories will be selected for urinalysis parameters (which are categorical in nature), for example, normal and abnormal.

The number and percentage of patients experiencing clinically significant laboratory values will be summarized by treatment within parameter type and analyte (chemistry, hematology, or urinalysis) during the Treatment Phase.

6.4.3 Electrocardiogram

Electrocardiogram (ECG) results will be summarized for patients in the safety population.

The number and percentage of patients with each result (normal or abnormal and not clinically significant, abnormal and clinically significant) will be summarized by treatment group for each visit at which ECGs are to be performed (Screening, and Follow-up Phase Week 24).

ECG parameters (PR, QT, QTcB, QTcF, QRS, and RR intervals) at each visit and change from baseline in these parameters at each post-baseline visit will also be summarized descriptively by treatment group (N, mean, standard deviation, median, minimum, and maximum). Baseline will be defined as the last value collected before the first dose of study drug; change from baseline will be computed as the value at the post-baseline visit minus the value at baseline. The number and percentage of patients with notable QT and QTcB and QTcF interval prolongation (>450 ms, >480 ms, >500 ms) and change from baseline in these intervals (>30 ms increase, >60 ms increase) will also be displayed.

6.4.4 Vital Signs, Weight and Body Mass Index

Vital signs, including heart rate, weight and body mass index will be summarized for the safety population. Vital signs and weight are to be collected and body mass index computed at screening, baseline, and each visit throughout the treatment and Follow-up Phases.

Observed values at each visit and change from baseline at each post-baseline visit will be summarized descriptively by treatment group (N, mean, standard deviation, median, minimum, and maximum). Baseline will be defined as the last measurement before the first dose of study drug; change will be defined as the post-baseline value minus the baseline value.

6.4.5 Physical Examination

Physical examination results will be summarized for patients in the safety population.

At screening, the number and percentage of patients with each result (normal, abnormal and not clinically significant, abnormal and clinically significant) will be summarized by treatment group for each body system to be examined.

At baseline and all post-baseline visits at which the physical exam is to be performed (Treatment Phase Weeks 4 and 12, Follow-up Phase Week 24, and end of study, the number and percentage of patients with each result (no change from the previous exam, change from the previous exam and not clinically significant, or change from the last exam and clinically significant) will be summarized by treatment group for each body system to be examined.

6.5 Interim Analysis

No formal interim analyses are planned, however, interim administrative analyses may be performed. If such administrative analyses are performed, only a limited number of individuals within the sponsor or designate organizations, none of whom will be involved in the day to day management of the current study, will have access to the results. If such administrative analyses are performed a stand-alone statistical analysis plan will be created. At the time of this SAP, no interim analyses are planned for the study.

6.6 Data Safety Monitoring Board Charter

This study will be monitored by an independent DSMB, which will conduct ongoing safety reviews of blinded study data to assess the emerging safety profile of BP3304. Serious adverse event data will be forwarded to the DSMB on an ongoing basis as the sponsor is notified.

The DSMB will have regularly scheduled teleconferences and/or meetings to review aggregate safety data which reflect the progress of the study. It is anticipated that these teleconferences and/or meetings will be at least quarterly during the enrollment phase of the study and when the study reaches the following milestones:

- 50% of patients have completed the Treatment Phase
- All patients have completed the Treatment Phase
- All patients have completed the Week 24 visit of the Follow-up Phase

The DSMB will not participate in any administrative reviews of exploratory efficacy data and will not have the authority to stop the study for futility reasons. The activities and responsibilities of the DSMB, including the frequency of teleconferences and/or meetings, will be described in detail in a separate DSMB charter which will be created as a document independent of this SAP.

7. TABLES, LISTINGS, AND FIGURES

All tables and listings will be displayed in landscape orientation, using Times Roman 10-point font. The top margin should be 1.25", and all other margins should be 1".

8. REFERENCES

Not applicable.