

Statistical Analysis Plan

A Prospective Randomized Placebo Controlled Study to Evaluate the Effect of Celecoxib on the Efficacy and Safety of Amlodipine on Renal and Vascular Function in Subjects with Existing Hypertension Requiring Antihypertensive Therapy

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APPROVAL SIGNATURE(S)

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Protocol No. KIT-302-03-02


I have read this SAP and confirm that to the best of my knowledge it accurately describes the statistical analyses for this study.

Sponsor Signatory:


.....

..... 20 April 2018
Date

Statistician Signatory:


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..... 20/APR/2018
Date

ABBREVIATIONS

| | |
|----------------------|---|
| ABPM | ambulatory blood pressure monitor |
| ADR | Adverse Drug Reaction |
| AE | Adverse Event |
| ANCOVA | Analysis of Covariance |
| ANOVA | Analysis of Variance |
| ATC | Anatomical Therapeutic Chemical |
| BE | bioequivalence |
| BLQ | below limit of quantification |
| BMI | Body Mass Index |
| BP | blood pressure |
| BUN | Blood urea nitrogen |
| Ca | calcium |
| CI | Confidence Interval |
| CRF | Case Report Form |
| CRO | Contract Research Organization |
| CS | Clinically Significant |
| DBP | diastolic blood pressure |
| DBP _{24h} | average 24-hour ambulatory diastolic blood pressure |
| DBP _{day} | average daytime (9:00 to 21:00) ambulatory diastolic blood pressure |
| DBP _{night} | average night-time (01:00 to 06:00) ambulatory diastolic blood pressure |
| DDI | drug-drug interaction |
| ECG | electrocardiogram |
| FCDP | fixed combination drug product |
| IB | Investigator's Brochure |
| ITT | Intent-To-Treat |
| LLOQ | Lower Limit of Quantification |
| LOCF | last observation carried forward |
| MedDRA | Medical Dictionary for regulatory activities |
| mITT | modified intent-to-treat |
| NCS | Not clinically significant |
| NSAID | non-steroidal anti-inflammatory drug |
| OE | over-encapsulated |
| PI | Principal Investigator |
| PK | Pharmacokinetic |
| PP | Per-Protocol |
| PT | Preferred Term |
| PTAE | pre-treatment adverse event |
| qd | once a day |
| SAE | Serious Adverse Event |
| SAP | Statistical Analysis Plan |
| SAS | Statistical Analysis System |
| SBP | systolic blood pressure |
| SBP _{24h} | average 24-hour ambulatory systolic blood pressure |
| SBP _{day} | average daytime (9:00 to 21:00) ambulatory systolic blood pressure |
| SBP _{night} | average night-time (01:00 to 06:00) ambulatory systolic blood pressure |
| SD | Standard Deviation |
| SOC | System Organ Class |
| TEAE | Treatment Emergent Adverse Event |
| UAE | Unexpected adverse event |
| UV | ultraviolet |
| WHO-DD | World Health Organization-Drug Dictionary |

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1. Introduction

This Statistical Analysis Plan (SAP) describes statistical analyses for KIT-302-03-02 study.

1.1. Background

KIT-302 is an oral fixed combination drug product (FCDP) consisting of the non-steroidal anti-inflammatory drug (NSAID) celecoxib and the calcium (Ca) channel blocker antihypertensive drug amlodipine besylate. KIT-302 is being developed as a “convenience reformulation” FCDP intended to facilitate and improve patient compliance with the once a day (qd) administration of its individual components, amlodipine and celecoxib, when used together for the intended patient population. It is also intended to provide prescribers with detailed data on how the combination affects the antihypertensive effect of the calcium channel blocker.

The proposed indications in the usage section of the KIT-302 product labeling are anticipated to read as follows: “KIT-302 is indicated for patients who require the use of a NSAID for chronic treatment for the relief of the signs and symptoms of osteoarthritis and who also require the treatment of hypertension to lower blood pressure. Lowering blood pressure reduces the risk of fatal and nonfatal cardiovascular events, primarily strokes and myocardial infarctions.” KIT-302 is not indicated to treat any other type of pain, and is not indicated for short term or intermittent treatment of osteoarthritis.

The formulation of KIT-302 consists of celecoxib and amlodipine besylate co-formulated in a single immediate release tablet. The dosage form was developed so that it would show bioequivalence (BE) to the individually marketed prescription celecoxib capsules and amlodipine besylate tablets given together.

In 2015, Kitov completed a phase 3 pivotal study (KIT-302-03-01) comparing amlodipine besylate monotherapy at a dose of 10 mg/day [over-encapsulated (OE) 10 mg amlodipine tablet + matched placebo for OE celecoxib capsule], with the combination of the components of KIT-302 at a dose of 10 mg amlodipine plus 200 mg celecoxib/day (OE 10 mg amlodipine tablet + OE 200 mg celecoxib capsule). The study also included a double placebo arm and a celecoxib monotherapy arm at a dose of 200 mg/day (matched placebo for OE amlodipine tablet + OE 200 mg celecoxib capsule). Adult subjects with newly diagnosed hypertension who required pharmacological therapy to control their hypertension were randomized to one of the four treatment arms and treated for two weeks. Subjects underwent 24-hour ambulatory blood pressure monitoring at baseline, during the initial 24 hours of therapy, after one week of therapy and after two weeks of therapy.

Study No. KIT-302-03-01 documented that while celecoxib had a negligible effect on blood pressure (BP), and amlodipine reduced BP significantly, adding celecoxib to the amlodipine did not impair the antihypertensive effects of amlodipine but rather tended to enhance amlodipine’s effect, although the synergistic effect only reach statistical significance for average night-time (01:00 to 06:00) ambulatory diastolic blood pressure (DBP_{night}) and average 24-hour ambulatory diastolic blood pressure (DBP_{24h}). The trending towards a synergistic antihypertensive effect was an unexpected finding, however this finding was consistent throughout the study’s data whether measuring daytime or night-time systolic blood pressure (SBP) or diastolic blood pressure (DBP), and whether measuring BP by using the ambulatory blood pressure monitor (ABPM) device or by taking the measurement manually in the clinic. This internal consistency strongly suggested that the effect is real. Study No. KIT-302-03-02 was designed to confirm this effect.

In attempting to explain the synergistic antihypertensive effect, a review of the plasma concentrations of amlodipine in the two amlodipine-receiving treatment arms was performed. This analysis documented a lower plasma concentration of amlodipine in the treatment arm receiving both celecoxib and amlodipine compared to the treatment arm receiving only amlodipine. It can therefore be concluded

that the enhanced antihypertensive effect when celecoxib was added was not due to an increased amlodipine plasma concentration through some pharmacokinetic (PK) drug-drug interaction (DDI).

An alternative explanation for the antihypertensive synergistic effect may be found in the renal data. Specifically, although patients treated with amlodipine had improved renal function as evidenced by a decreased serum creatinine, there was a trend towards an even greater reduction in serum creatinine among patients treated with both amlodipine and celecoxib. Such an enhancement in renal function might be expected to improve BP control and thus, at least partially explains the synergistic antihypertensive effect. However, since this renal synergy did not reach statistical significance, confirmation would require future clinical investigations. Study No. KIT-302-03-02 was designed to confirm this effect.

Further evidence for a renal component in the synergistic antihypertensive effect can be identified in the adverse event (AE) tables. Specifically, patients treated with amlodipine had a nearly 16% reporting rate of peripheral oedema; such an adverse reaction has been a long-recognized side effect of amlodipine. However, among those patients receiving both amlodipine and celecoxib, the rate of reported peripheral oedema was nearly halved. Thus, it would appear possible that the addition of celecoxib to amlodipine is in some way acting as a diuretic, thereby preventing the peripheral oedema and thus, enhancing the antihypertensive effect. Since this indirect measure of renal synergy did not reach statistical significance, confirmation would require future clinical investigations. Study No. KIT-302-03-02 was designed to confirm this effect.

1.2. Statistical Analysis Plan Summary

This Statistical Analysis Plan (SAP) describes the statistical analysis for the KIT-302-03-02 study. The SAP provides full details of the analyses, the data displays and the algorithms to be used for data derivations. The analysis will be done using statistical software Statistical Analysis System (SAS) version 9.4 or higher.

1.3. Changes from Protocol

The following statistical analysis changes from the protocol will be implemented:

1.3.1. Validity of ABPM measurements

Section 10.7 of the protocol defines an ABPM measurement as valid based on the following six criteria:

- a. The time of the first study measurement is between 07:00 and 10:00.
- b. The duration, from the first study measurement to the last study measurement, is at least 25 h (1500 min).
- c. There are at least 21 study measurements recorded during the standard daytime period (09:00 to 21:00).
- d. There are at least 8 study measurements recorded during the standard night-time period (01:00 to 06:00).
- e. There are at least 35 study measurements recorded after the white-coat window.
- f. There are no more than 3 hours with a total measurement weight of less than 20 min and no more than 2 consecutive hours with total measurement weights each of less than 20 min.

For the efficacy analysis, the validity of ABPM measurements will instead be based on valid daytime measurements (i.e., bullet c), as the remainder of the period has no effect on the primary endpoint, which is average daytime (9:00 to 21:00) ambulatory systolic blood pressure (SBP_{day}). Thus, all ABPM measurements with an assigned day validity of valid will be considered valid, regardless of the assigned night, 24h, overall, or other validities.

The impact of redefining a valid ABPM measurement based only on the validity of the daytime measurements (i.e., bullet c) is that the analyses of the secondary ABPM efficacy parameters [average 24-hour ambulatory systolic blood pressure (SBP_{24h}) and DBP_{24h}] and exploratory ABPM efficacy parameters [average night-time (01:00 to 06:00) ambulatory systolic blood pressure (SBP_{night}) and DBP_{night}] may include invalid measurements with respect to the 24-hour period (i.e., may not meet criterion d or e) or night-time period (i.e., may not meet criterion d), respectively. It is anticipated that this will be a very small number of cases and will not impact the secondary and exploratory efficacy conclusions drawn. Sensitivity analyses will be conducted to verify this point (see Section 1.3.3.1 below).

It should be noted that for establishing eligibility, the validity of the ABPM continued to be based on the definition of ABPM validity in the protocol. Thus, in order to be enrolled, subjects had to have a baseline ABPM that met all of the criteria above (a, b, c, d, e, and f).

Documentation of the individual validity criteria Dabl applied to assign overall, daytime, nighttime, 24h, and other ABPM validity flags is provided in “Note to File – Link of Individual Protocol-Specified ABPM Validity Criteria to Dabl Daytime, Nighttime, and 24h Validity Flags”, a copy of which is available in the Trial Master File.

1.3.2. Definition of Intent-to-Treat (ITT) and Modified Intent-to-Treat (mITT) populations

The definition of the ITT population as stated in the protocol was at risk of losing randomized subjects and will be changed to remain faithful to the ITT principal. The ITT population will include all randomized subjects with a valid ABPM measurement at Baseline (according to the definition of validity described in Section 1.3.1 above). The protocol definition requires valid Baseline and valid follow-up ABPM measurements, either Day 6 or Day 13. This definition will instead be used for a mITT population, and the mITT population will be used for sensitivity analyses (see Section 1.3.3.2 below).

1.3.3. Sensitivity analyses

1.3.3.1. Sensitivity analysis for the validity of ABPM measurements

The following sensitivity analyses will be performed to verify that redefining a valid ABPM measurement based only on the validity of the daytime measurements (see Section 1.3.1 above for further detail) will not impact the secondary and exploratory ABPM efficacy conclusions drawn:

1. ITT for SBP_{24h} excluding SBP_{24h} values that had an entry of valid for day validity and an entry of invalid for night or 24h validity (i.e., did not meet criterion d or e, respectively)
2. ITT for DBP_{24h} excluding DBP_{24h} values that had an entry of valid for day validity and an entry of invalid for night or 24h validity (i.e., did not meet criterion d or e, respectively)
3. ITT for SBP_{night} excluding SBP_{night} values that had an entry of valid for day validity and an entry of invalid for night validity (i.e., did not meet criterion d)
4. ITT for DBP_{night} excluding DBP_{night} values that had an entry of valid for day validity and an entry of invalid for night validity (i.e., did not meet criterion d)

1.3.3.2. Sensitivity analysis of ITT versus mITT population

A sensitivity analysis will be conducted to insure the change in definition of the ITT population (see Section 1.3.2 above) does not impact the study conclusions. A mITT population will be based on the definition originally presented as the ITT population in the protocol (valid Baseline and at least one valid follow-up ABPM measurement) and a second set of analyses will be conducted purely to demonstrate the definition does not have an impact on the primary and secondary efficacy analyses. The following analyses will be conducted:

1. mITT for SBP_{day}
2. mITT for SBP_{24h}
3. mITT for DBP_{24h}

1.3.3.3. Sensitivity analysis of baseline effect

To assess the impact of baseline, a further sensitivity analysis will be conducted on the primary endpoint (mean change of SBP_{day}) using a regression model adjusted from Baseline on ITT, mITT, and per-protocol (PP) populations.

1.3.4. Exploratory efficacy analyses

Exploratory efficacy analyses will be conducted to investigate the potential effect of treatment on:

1. SBP_{night}
2. DBP_{night}
3. Average daytime (9:00 to 21:00) ambulatory diastolic blood pressure (DBP_{day})

These analyses will include two-sample t-tests to test one-side hypotheses of superiority for pairwise comparisons between treatment arms 1 and 2, 1 and 3, and 2 and 3.

Further, two-sample t-tests to test one-side hypotheses of superiority for pairwise comparisons between treatment arms 1 and 3 and 2 and 3 will be performed for SBP_{day}, SBP_{24h}, and DBP_{24h}. The comparison of treatment arms 1 and 2 for these endpoints are covered separately under the respective primary and secondary efficacy analyses.

All exploratory efficacy analyses will be conducted on the ITT population including LOCF (and MMRM if possible) for subjects who were withdrawn from treatment early. Sensitivity analyses will be used to compare these results to those of the PP data set.

1.3.5. Definition of one-sided confidence interval (CI)

For clarity, the non-inferiority trial will be based on comparing the change from baseline to end of study for the OE amlodipine besylate tablet and OE celecoxib capsule arm (treatment arm 1) minus $0.5 * \delta$ the OE amlodipine besylate tablet and matched placebo for OE celecoxib capsule arm (treatment arm 2) with 0. A one-sided 97.5% CI for δ will be computed. This is consistent and equivalent with the hypothesis section of the protocol, which states that the primary efficacy endpoint will be that the lower limit of the 95% CI for SBP_{day} reduction in treatment arm 1 will be at least 50% of the mean reduction in treatment arm 2. This statement is to clear up places in the protocol and SAP that conceptually state the comparison in less technical language.

1.3.6. Analysis populations

In addition to adding the mITT population noted above, a Randomized population (defined as all randomized subjects) will be added to produce all listings, except for screening failures and the listing of plasma amlodipine concentrations. The Randomized population will also be used to produce a summary tabulation of the number and percentage of subjects who completed the study and who discontinued the study after randomization by treatment arm and overall, and the number and percentage of patients with a given primary reason for discontinuation (AE, withdrawal of consent, lost to follow-up, protocol violation, study terminated, or other) by treatment arm and overall. The Randomized population will also be used to produce a summary tabulation of the number of subjects in the randomized population, the ITT population, the mITT population, the PP population, the safety population, and the PK population.

An Overall Trial population (defined as all patients screened) will be added and used to produce the listing of screening failures, as well as a tabular summary of the number of patients at Initial Screening Visit, number of patients at Final Screening Visit, number of patients at Day 0 visit,

number of patients randomized, and number of patients at each of the remaining study visits (Days 6, 7, 13, 14 and 28) by treatment arm and overall.

The protocol includes a PK assessment at Day 14 for subjects enrolled at Investigational Sites that have ultraviolet- (UV-) shielded lights; however, a formal definition of the PK population for analysis was not included in the protocol. A definition of the PK population was added to the SAP (see Section 4.1). The listing of plasma amlodipine concentrations will use all subjects that were enrolled at an Investigational Site that had UV-shielded lights, and the PK population will be used for all analyses (tabular summaries and box plot).

1.3.7. Definition of change from baseline

For all efficacy endpoints, the mean change will be computed considering the difference between the value at endpoint and the value at baseline (Endpoint minus Baseline). The protocol states the mean change as baseline minus endpoint. This change does not affect the absolute value of the results but gives a more intuitive interpretation of the direction of change (i.e., with a negative value indicating a decrease in BP over time and a positive value indicating an increase in BP over time).

1.3.8. Peak and trough analyses

SBP and DBP at the expected peak and trough times for amlodipine for the ITT population at Day 6 and Day 13 will be summarized by treatment arm by descriptive statistics. Additionally, the difference between Day 6 and Day 13 will be summarized by treatment arm by descriptive statistics, and compared between treatment arms using t-test. No last observation carried forward (LOCF) will be used for this analysis. Details of how peak and trough measurements will be selected from the ABPM measurements are included in Section 7.10.

1.3.9. Safety analyses

a. Oedema events

A safety table extracting the occurrences of oedema events, which include treatment emergent adverse events (TEAEs) with preferred terms (PTs) of oedema, oedema peripheral, peripheral swelling, swelling, and joint swelling, from the adverse events table will be produced. See Section 7.9 for further detail. The rates of oedema events for treatment arms 1 and 2 will be reported and compared using exact logistic regression, reporting the odds ratio. The Fisher's exact test will be run to compare the number of oedema events that occurred while on treatment (Day 0 to Day 14+1) and post-treatment (>Day 14+1) between treatment arms 1 and 2.

b. Other PTs of interest

The protocol specified a comparison of AE rates for terms associated with hypotension, defined as dizziness, falls, light-headedness, and vertigo. The definition will be changed to TEAEs with PTs of orthostatic hypotension, fall, dizziness, dizziness postural, and vertigo. The use of PTs and the addition of orthostatic hypotension to the list provides a more precise and comprehensive analysis, as well as allows a direct comparison to a similar analysis conducted for the prior trial (KIT-302-03-01). Note, light-headedness is coded under dizziness as a PT.

c. Adverse drug reaction (ADR)

For the summary tabulations of TEAEs by assigned relationship to study drug, adverse reactions and suspected adverse reactions will be combined and presented as ADRs (i.e., pooled). The TEAE listing will continue to use the individual relationship assignments (i.e., adverse reaction, suspected adverse reaction, and unrelated), as specified in the protocol. The same approach was taken for the prior trial (KIT-302-03-01), and therefore, this change will allow for comparison across studies. A statistical evaluation of the rate of treatment-emergent ADRs among treatment arms using a Chi-

square test or Fisher's exact test (if more than 20% of the cells in a contingency table had expected counts less than 5) will be added.

d. Unexpected adverse event (UAE)

A tabulation of treatment-emergent UAEs (defined in Section 6.4) will be added. The summary will include the number of events, as well as the number and percentage of subjects. Subjects will be counted once per category [specific system organ class (SOC) or PT], regardless of the number of events that may have occurred for that patient in that category. The tabulation will be based on the respective **Principal Investigator (PI) assignments** of expectedness. A statistical evaluation of the rate of treatment-emergent UAEs among treatment arms using a Chi-square test or Fisher's exact test (if more than 20% of the cells in a contingency table had expected counts less than 5) will be performed.

As with the prior trial (KIT-302-03-01), there are several TEAEs designated as unexpected by one or more PIs for one or more subjects that the Sponsor considered as expected based on the product labelings for the study drugs, including dyspepsia, flatulence, vomiting, chest pain, pain (lower body pain), thirst, nasopharyngitis (cold symptoms), pharyngitis, sinusitis, alanine aminotransferase increased, increased appetite, arthralgia, back pain, joint swelling (swelling of knee), dizziness, headache, cough, epistaxis, dry skin, purpura, and rash.

Further, there were several TEAEs designated as expected by one or more PIs for one or more subjects that the Sponsor considered as unexpected as they were not listed in the product labelings for the study drugs and were not listed as expected AEs in the protocol, including toothache, seasonal allergy (hayfever symptoms), urinary tract infection, plantar fasciitis, dysphoria, epididymal cyst, blister, pigmentation disorder, feeling cold, and peripheral coldness. It should be noted that in the prior study (KIT-302-03-01), the Sponsor assigned pollakiuria as an unexpected event in error. Micturition frequency is listed in the labelings for both study drugs. As such, the Sponsor considers the pollakiuria events in this study and the prior study as expected.

The Sponsor's assignments of expectedness will be noted in the main body of the clinical study report, and a footnote will be added to the above tabular summary to clarify that it is based on the PI's assignments, which were not all consistent with the protocol-specified definition of UAE. A similar approach was taken for the prior trial (KIT-302-03-01), and thus will allow for comparison across studies. To facilitate the preparation of this text for the main body of the clinical study report, an analysis will be run based on the above expectedness changes (Sponsor's assignments), although, the table itself will not be included in the clinical study report.

e. Pre-treatment adverse events (PTAEs)

If there are no serious PTAEs or PTAEs that led to withdrawal, the respective protocol-specified tabular summaries will not be produced. The protocol-specified tabular summary of all PTAEs will be produced, regardless.

f. Exact logistic regression analyses of TEAEs and treatment-emergent serious adverse events (SAEs)

An exact logistic regression to compare TEAE rates between amlodipine + celecoxib and amlodipine + placebo, with the TEAE (1 = at least one TEAE occurred for the subject; 0 = otherwise) as the dependent variable, and treatment (amlodipine + celecoxib and amlodipine + placebo) as fixed effects, will be added.

An exact logistic regression to compare treatment-emergent SAE rates between amlodipine + celecoxib and amlodipine + placebo, with the treatment-emergent SAE (1 = at least one treatment-emergent SAE occurred for the subject; 0 = otherwise) as the dependent variable, and treatment

(amlodipine + celecoxib and amlodipine + placebo) as fixed effects, will be added, with the caveat that if there are no treatment-emergent SAEs, the tabular summary will not be produced.

g. Physical examination

The physical examination summary tabulation will be limited to the comprehensive physical examinations at the Initial Screening Visit and Day 14 and will not include the targeted physical examinations at Days 0, 7 and 28. The targeted physical examination findings will still be provided as a listing as specified in the protocol. A shift table presenting the number and the percentage of subjects in each bivariate category (Initial Screening Visit versus Day 14) with regards to Investigator's interpretation [normal, abnormal not clinically significant (NCS), abnormal clinically significant (CS), not done, and missing] by treatment arm will be done in place of a frequency only table. Due to the limited number of events, the comparisons among treatment arms using Chi-square, binomial, and logistic analyses will not be done since they would not provide meaningful analyses.

h. Vital signs

Descriptive statistics [n, mean, standard deviation (SD), median and range] will be added for the change from baseline at each visit (Days 7, 14, and 28) for each vital sign (clinic visit resting SBP and DBP, pulse rate, respiration rate, and oral body temperature) for the safety population. The protocol-specified comparisons among treatment arms using ANCOVA will be limited to SBP and DBP (and not performed for pulse rate, respiration rate, and oral body temperature). Further, the resting SBP and DBP ANCOVA comparisons will be limited to the change from baseline to Day 14 (and not evaluated for the change from baseline to Days 7 or 28) since the effect would be more limited after only 7 days, and since subjects would have been off study drugs for 14 days at Day 28. The LOCF method of imputation will be applied for missing values.

i. Orthostatic hypotension

Descriptive statistics (n, mean, SD, median and range) will be added for the change from baseline at each visit (Days 7 and 14) for the orthostatic hypotension BP measurements (i.e., SBP and DBP after supine 5 minutes, standing 1 minute and standing 3 minutes, as well as the respective differences between standing and supine) for the safety population. The protocol-specified comparisons of the orthostatic hypotension BP measurements among treatment arms using ANCOVA will be limited to the change from baseline to Day 14 (and not evaluated for the change from baseline to Day 7) since any effect is anticipated to be maximal at Day 14. Further, the comparisons of the orthostatic hypotension diagnoses among treatment arms will be limited to Chi-square test or Fisher's exact test (and will not include logistic analyses as noted in the protocol) due to the limited number of subjects.

j. Hematology, serum chemistry, and urinalysis

For the majority of the hematology, serum chemistry, and urinalysis tests, the comparisons of the safety population data among treatment arms using Chi-square, binomial, and logistic analyses for dichotomous variables (e.g., negative/positive) and ANCOVA for continuous variables will not be done due to the limited number of subjects. The exceptions are serum creatinine and blood urea nitrogen (BUN), where comparisons between treatment arms will be performed using an ANCOVA model with change from baseline to Day 14 as the dependent variable, treatment as the fixed effect, and baseline as the covariate.

The laboratory reference range for assigning low "L" flags to the creatinine clearance results differed for the Celerion, Belfast laboratory (>90 mL/min) versus the centralized laboratory used for the remaining sites (ACM Global Central Laboratories; ≥ 60 mL/min). The serum chemistry shift table analysis will be based on the laboratory assigned flags (i.e., no reassignment of the Celerion, Belfast laboratory flags based on the ACM laboratory reference range will be made). The main body of the clinical study report will note the difference in the creatinine clearance reference range for the two

laboratories and will note by treatment group any cases where a Celerion, Belfast low creatinine clearance value would be reassigned as Normal if the ≥ 60 mL/min criterion was used.

Documentation of the differing creatinine clearance reference ranges for ACM and Celerion, Belfast is included in Appendix 16.1.10 of the clinical study report and in the individual subject laboratory reports that are included with the consolidated case report form PDF files, copies of which are included in the Trial Master File.

k. Electrocardiogram (ECG)

For analysis of ECG assessments, a shift table presenting the number and the percentage of subjects in each bivariate category (Initial Screening Visit versus Day 14) with regards to Investigator's interpretation (normal, abnormal NCS, abnormal CS, not done) by treatment arm will be done in place of a frequency only table. The protocol-specified comparisons among treatment arms using Chi-square, binomial, and logistic analyses will not be done since, based upon what is already known about amlodipine and celecoxib and what was demonstrated in the prior trial (KIT-302-03-01), minimal ECG effects are anticipated.

1.3.10. BLQ computation for plasma concentration

The protocol specifies that all plasma amlodipine concentration values below the lower limit of quantification (LLOQ) will be reported as zero. This will be modified as follows:

For the individual patient data listing of amlodipine plasma concentrations, all values below the LLOQ will be reported as below the limit of quantitation (BLQ), as in the bioanalytical report [Determination of Amlodipine in human plasma (lithium heparin) samples from "A Prospective Randomized Placebo Controlled Study to Evaluate the Effect of Celecoxib on the Efficacy and Safety of Amlodipine on Renal and Vascular Function in Subjects with Existing Hypertension Requiring Antihypertensive Therapy" by LC-MS/MS, bioanalytical report amendment number ACA20019 Am 1, Celerion Switzerland AG, March 22, 2018].

For the summary of non-transformed amlodipine plasma concentration values by treatment group by descriptive statistics (n, mean, SD, median, and range), as well as the t-test analysis of the non-transformed values and the box plot analysis of non-transformed values, all BLQ values will be treated as zero.

For the summary of log-transformed amlodipine plasma concentration values by treatment group by descriptive statistics (n, mean, SD, median, and range), as well as the t-test analysis of the log-transformed values, all BLQ values will be treated as 0.04 ng/mL rather than 0. Zero cannot be log-transformed. Assignment of the BLQ values to a nonzero number will allow computation of the log transformation. The selection of 0.04 ng/mL as the nonzero number for BLQ assignment was based on the LLOQ of the validated bioanalytical method [i.e., 0.05 ng/mL; Validation of an LC/MS/MS Method for the Determination of Amlodipine in Human Plasma (Li Heparin), method validation report number VZZ00140-01, MDS Pharma Services Switzerland AG, July 5, 2006; Validation of an LC-MS/MS Method for the Determination of Amlodipine in Human Plasma (Lithium Heparin), method validation report number VZZ46541, Celerion Switzerland AG, January 20, 2016] and selecting the next lowest number at the hundredth decimal place.

1.3.11. Sample size formula

Changed the α (one-sided level of significance) in the sample size formula to 0.025. The protocol listed 0.05 in error. The planned number of subjects (approximately 105) was based on the 0.025 value.

1.3.12. Demographic and baseline characteristics

A summary tabulation for the Safety Population, including demographic characteristics (age, sex and race), Initial Screening Visit characteristics [height, weight, body mass index (BMI), pulse rate,

respiration rate, oral body temperature, SBP left arm, SBP right arm, DBP left arm, DBP right arm, and ECG], and Baseline Day 0 characteristics (weight, SBP, and DBP) by treatment arm and overall will be added. The Day 0 SBP and DBP to be included in this table will be for the arm with the higher average resting SBP determined as part of the manual vital signs at the Initial Screening Visit (i.e., the arm used for all ABPM and manual vital sign assessments throughout the remainder of the study). Descriptive statistics will be generated as appropriate (i.e., n, mean, SD, median and range for continuous data and number and percentage of patients for categorical data).

1.3.13. Investigational site-specific analyses

An Investigational Site-specific summary tabulation for the Safety Population, including demographic characteristics (age, sex and race), Initial Screening Visit characteristics (height, weight, BMI, pulse rate, respiration rate, oral body temperature, SBP left arm, SBP right arm, DBP left arm, DBP right arm, and ECG), and Baseline Day 0 characteristics (weight, SBP, and DBP) by treatment arm and overall will be added. The Day 0 SBP and DBP to be included in this table will be for the arm with the higher average resting SBP determined as part of the manual vital signs at the Initial Screening Visit. Descriptive statistics will be generated as appropriate (i.e., n, mean, SD, median and range for continuous data and number and percentage of patients for categorical data).

An Investigational Site-specific summary tabulation for the Safety Population, including SBP_{day}, SBP_{night}, SBP_{24h}, DBP_{day}, DBP_{night} and DBP_{24h} at baseline (Day -1 to Day 0) by treatment arm and overall will be added. The summary will include pooled values (i.e., for all sites) as well. Descriptive statistics will be generated (i.e., n, mean, SD, median and range).

A summary tabulation for the ITT Population, including the mean \pm SD SBP_{day} at baseline, end of study, and the change from baseline to end of study for the patients at Sites 301 (Queen Mary School of Medicine & Dentistry), 302 (Celerion, Belfast), 303 (Rowden Surgery), and 304 (Medicines Evaluation Unit), the four largest recruiting sites, and the patients at all remaining sites (pooled) by treatment arm will be added as a means of evaluating the comparability of the primary efficacy endpoint across sites. Pooling of data for 4 of the 8 sites (that randomized patients) will be done due to the small numbers of patients per treatment arm per Investigational Site. The table will also include a row that includes the summary statistics for the whole ITT population (i.e., including all sites) for comparison.

1.3.14. Past and concomitant diseases

Summary tabulations for the Safety Population, including the number and percentage of subjects with past and concomitant diseases by SOC and PT, and further categorized by treatment arm will be added.

Past diseases will be defined as medical conditions that initiated and ended prior to the Initial Screening Visit (i.e., any disease/history listed on the “Cardiovascular History” or “Medical History and/or Concomitant Diseases” case report forms (CRFs) that has a stop date that is prior to the Initial Screening Visit date, if a stop date is available, and that has “no” checked for “Ongoing”; any surgery listed on the “Surgical History” CRF that has a date that is prior to the Initial Screening Visit date).

Concomitant diseases will be defined as medical conditions that were ongoing at the Initial Screening Visit (i.e., any disease/history listed on the “Cardiovascular History” or “Medical History and/or Concomitant Diseases” CRFs that has no stop date entered and that has “yes” checked for “Ongoing”; any surgery listed on the “Surgical History” CRF that has a date equal to the Initial Screening Visit date). Any disease that initiates after completion of the Initial Screening Visit and before administration of the first dose of study drugs (Day 0) will be recorded as a PTAE (and will not be considered as a concomitant disease for this analysis).

Past and concomitant diseases will be coded using Medical Dictionary for Regulatory Activities (MedDRA). Patients will be counted once per SOC category, regardless of the number of diseases/PTs they had within that SOC category.

1.3.15. Previous medications

A summary tabulation for the Safety Population, including the number and percentage of subjects with previous medications by Anatomical Main Group [1st level of the Anatomical Therapeutic Chemical (ATC) classification], Chemical Subgroup (4th level of the ATC classification) and Preferred Name, and further categorized by treatment arm will be added. Per protocol, all medications taken within 30 days prior to the Initial Screening Visit were to be recorded. Previous medications will be coded using the World Health Organization-Drug Dictionary (WHO-DD).

Previous medications will be defined as medications with a start date < date of first randomized study drug intake and a stop date < date of first randomized study drug intake.

In case of missing or partial dates, a set of rules for the imputation method is described in Section 5.

1.3.16. Concomitant, posterior, and unclassified medications

A summary tabulation for the Safety Population, including the number and percentage of patients with concomitant medications by Anatomical Main Group, Chemical Subgroup and Preferred Name, and further categorized by treatment arm will be added. Per protocol, all medications taken from the first dose of study drugs (Day 0) through the final study visit assessment were to be recorded; therefore, the concomitant medications tabulation will not include medications that started after the final study visit assessment. Concomitant medications will be coded using the WHO-DD.

Concomitant medications will be defined as medications (other than the study drugs) with either:

- a) a **start date** \geq date of first randomized study drug intake and \leq date of final study visit assessment; or
- b) a **start date** < date of first randomized study drug intake and a **stop date** \geq date of first randomized study drug intake

Posterior medications will be defined as medications with a start date > date of final study visit assessment.

For the medications listing, medications will be classified as either Type 1 (previous medication), Type 2 (concomitant medication), Type 3 (posterior medication), or Type 4 (unknown). Tabular summaries will be prepared for each classification (i.e., previous medications (see Section 1.3.15), concomitant medications, posterior medications, and medications that could not be classified as previous, concomitant, or posterior due to unknown or partial start or stop dates). If there are no Type 4 medications, then the corresponding tabular summary will not be produced.

In case of missing or partial dates, a set of rules for the imputation method is described in Section 5.

1.3.17. Treatment compliance and extent of exposure

A summary tabulation for the Safety Population, including treatment compliance and extent of exposure by treatment arm and overall will be added. The total number of white capsules (celecoxib or matched placebo) taken, total number of orange capsules (amlodipine or matched placebo) taken, percentage of white capsule planned dose taken (out of 14 capsules), percentage of orange capsule planned dose taken (out of 14 capsules) and total treatment duration will be summarized by descriptive statistics for continuous variables (n, mean, SD, median and range). The percentage of white capsule planned dose taken and percentage of orange capsule planned dose taken will also be

summarized by category (i.e., <75%, 75%≤X<100% and 100%) using descriptive statistics for categorical data (number and percentage of patients).

1.3.18. Hierarchical analysis of secondary efficacy endpoints

Per the protocol, a serial gatekeeping strategy was to be used to evaluate the effect of amlodipine tablets (10 mg) and celecoxib capsules (200 mg) given together on the secondary efficacy endpoints. If and only if the statistical significance was achieved for the primary efficacy endpoint, the secondary hierarchical analysis was to be used to evaluate the secondary endpoints (i.e., body weight, SBP_{24h}, DBP_{24h}, and creatine clearance) and was only to proceed to the next endpoint in the list if the alpha is met for the prior analyses. While defining success at the secondary efficacy level will remain based on the hierarchical approach, regardless of the outcome, all four secondary efficacy endpoints (body weight, SBP_{24h}, DBP_{24h}, and creatine clearance) will be analyzed for informational purposes and to allow comparisons to the trends and statistically significant differences observed in the prior trial (KIT-302-03-01).

1.4. Study Summary

This is a prospective randomized placebo controlled study to evaluate the effect of celecoxib on the efficacy and safety of amlodipine on renal and vascular function in subjects with existing hypertension requiring antihypertensive therapy.

1.5. Version History

SAP v0.1 – Draft version (May 12, 2017).

SAP v1.1 – Draft version (August 30, 2017)

SAP v2.1 – Draft version (October 9, 2017)

SAP v3.0 – Final version pre-unblinding (October 12, 2017)

SAP v4.0 – Final version post-unblinding (April 20, 2018)

Specifications are based on the following documents:

- Study protocol (Version 4: December 16, 2016)
- CRF (Version 1.4, April 13, 2017)

2. Study Objectives and Endpoints

2.1. Primary Objective(s)

Efficacy:

The primary efficacy objective of this study is to demonstrate that the mean reduction in SBP_{day} after oral administration of amlodipine tablets (10 mg) and celecoxib capsules (200 mg) given together qd for 14 days in adult subjects with existing hypertension is no less than half the mean reduction in SBP_{day} after oral administration of amlodipine tablets (10 mg) given alone (i.e., with matched celecoxib placebo) qd for 14 days in the same population.

2.2. Secondary Objective(s)

Efficacy:

The secondary objectives of this study are as follows:

1. To evaluate the effect of amlodipine tablets (10 mg) and celecoxib capsules (200 mg) given together qd for 14 days in adult subjects with existing hypertension on secondary efficacy endpoints using a serial gatekeeping strategy. If and only if the primary efficacy endpoint is

statistically achieved, a secondary hierarchical analysis will be used to evaluate the endpoints listed below, and will only proceed to the next endpoint in the list if the alpha is met for the prior analyses.

- a. Difference in mean change in body weight from baseline to end of treatment between treatment arms [amlodipine tablets (10 mg) and celecoxib capsules (200 mg) given together, amlodipine tablets (10 mg) given alone (with matched celecoxib placebo), and placebo];
 - b. Difference in the mean reduction in SBP_{24h} from baseline to end of treatment between amlodipine tablets (10 mg) and celecoxib capsules (200 mg) given together and amlodipine tablets (10 mg) given alone (with matched celecoxib placebo) treatment arms;
 - c. Difference in the mean reduction in DBP_{24h} from baseline to end of treatment between amlodipine tablets (10 mg) and celecoxib capsules (200 mg) given together and amlodipine tablets (10 mg) given alone (with matched celecoxib placebo) treatment arms;
 - d. Difference in the mean change in creatinine clearance from baseline to end of treatment between amlodipine tablets (10 mg) and celecoxib capsules (200 mg) given together and amlodipine tablets (10 mg) given alone (with matched celecoxib placebo) treatment arms.
2. To evaluate the safety of amlodipine tablets (10 mg) and celecoxib capsules (200 mg) given together qd for 14 days in adult subjects with existing hypertension.
 3. To evaluate the effect of celecoxib on the mean plasma concentrations of amlodipine in adult subjects with existing hypertension after 14 days of treatment with amlodipine tablets (10 mg) and celecoxib capsules (200 mg) given together compared to amlodipine tablets (10 mg) given alone (with matched celecoxib placebo).

2.3. Primary Endpoint(s)

Efficacy:

The primary efficacy endpoint for this trial is the difference in the mean reduction in SBP_{day} from the baseline (Day -1 to Day 0) ABPM measurement to the final (Day 13 to Day 14) ABPM measurement, where a subject completes the 14-day treatment plan, or to the Day 6 to Day 7 ABPM measurement, where a subject is withdrawn from treatment at Day 7, between subjects treated with amlodipine tablets (10 mg) and celecoxib capsules (200 mg) given together (arm 1) and amlodipine tablets (10 mg) given alone (i.e., with matched celecoxib placebo) (arm 2).

The primary efficacy endpoint is that the lower limits of the 97.5% one-sided CI for the difference in SBP_{day} reduction in treatment arm 1 and 50% of the mean reduction in treatment arm 2 is less than 0. Note, as detailed in section 6.7, because the preferred outcome is a larger reduction, a negative value indicates a larger reduction in arm 1 as compared to arm 2.

2.4. Secondary Endpoint(s)

Efficacy:

Subjects were to be randomized 3:3:1 to one of three treatment arms:

1. OE 10 mg amlodipine besylate tablet + OE 200 mg celecoxib capsule;
2. OE 10 mg amlodipine besylate tablet + matched placebo for OE celecoxib capsule;
3. Matched placebo for OE amlodipine tablet + matched placebo for OE celecoxib capsule.

A serial gatekeeping strategy was to be used to evaluate the effect of amlodipine tablets (10 mg) and celecoxib capsules (200 mg) given together on secondary efficacy endpoints. If and only if the

statistical significance was achieved for the primary efficacy endpoint, a secondary hierarchical analysis was to be used to evaluate the endpoints listed below, and was only to proceed to the next endpoint in the list if the alpha is met for the prior analyses.

1. Difference in mean change in body weight from baseline (Day 0) to Day 14 measurement (or if a LOCF is required, the Day 7 measurement) between treatment arms [amlodipine tablets (10 mg) and celecoxib capsules (200 mg) given together (arm 1), amlodipine tablets (10 mg) given alone (with matched celecoxib placebo) (arm 2), and placebo (arm 3)];
2. Difference in the mean reduction in SBP_{24h} from the baseline (Day -1 to Day 0) ABPM measurement to the Day 13 to Day 14 ABPM measurement (or if a LOCF is required, the Day 6 to Day 7 ABPM measurement) between subjects treated with amlodipine tablets (10 mg) and celecoxib capsules (200 mg) given together (arm 1) and amlodipine tablets (10 mg) given alone (with matched celecoxib placebo) (arm 2);
3. Difference in the mean reductions in DBP_{24h} from the baseline (Day -1 to Day 0) ABPM measurement to the Day 13 to Day 14 ABPM measurement (or if a LOCF is required, the Day 6 to Day 7 ABPM measurement) between subjects treated with amlodipine tablets (10 mg) and celecoxib capsules (200 mg) given together (arm 1) and amlodipine tablets (10 mg) given alone (with matched celecoxib placebo) (arm 2);
4. Difference in the mean change in creatinine clearance from baseline (Day 0) to the Day 14 measurement (or if a LOCF is required, the Day 7 measurement) between subjects treated with amlodipine tablets (10 mg) and celecoxib capsules (200 mg) given together (arm 1) and amlodipine tablets (10 mg) given alone (with matched celecoxib placebo) (arm 2).

3. Study Design

This is a multi-center, randomized, double blind, placebo controlled trial to evaluate the effect of celecoxib on the efficacy, safety, and pharmacokinetics of amlodipine in subjects with existing hypertension requiring antihypertensive therapy.

Approximately 105 adult subjects who required and were currently using pharmacological therapy with a single agent that was not a calcium channel blocker to control their hypertension were to be randomized 3:3:1 to one of three treatment arms:

1. OE 10 mg amlodipine besylate tablet + OE 200 mg celecoxib capsule;
2. OE 10 mg amlodipine besylate tablet + matched placebo for OE celecoxib capsule;
3. Matched placebo for OE amlodipine tablet + matched placebo for OE celecoxib capsule.

All drugs were to be administered orally qd for 14 days (Days 0-13) for a total of 14 doses. With the exception of Day 0, when study drug intake was to be after determination of eligibility (and at least 25 hours after the Day -1 ABPM is initiated), Days 6 and 13, when study drug intake was to be at the time of fitting the ABPM (following fitting) and Day 7, when study drug intake was to be 24 h \pm 1 h after the Day 6 dose, the subjects were to be instructed to take the study drugs between 07:00 and 10:00, and preferably at approximately the same time each day.

Initial Screening Visit (Day -14 to -10): Each subject was to be provided with oral and written information (ICF) describing the study and have any questions answered. Subjects that consented in writing to participate in the study were to undergo eligibility assessments, including complete medical history, comprehensive physical examination, height, body weight in underwear and light gown, BMI,

vital signs (BP, pulse rate, respiration rate, and oral body temperature), 12-lead ECG, hematology, serum chemistry, urinalysis, serum pregnancy test for women of childbearing potential (WCBP), urine drug screen, and record medications taken within 30 days prior to initial screening visit.

Subjects who met eligibility criteria based on the above initial screening visit procedures were to be instructed to cease taking their current BP medication. Monitoring for PTAEs was to begin upon completion of the initial screening visit procedures and continue through the 9 to 13 days of washout, the final screening visit on Day -1, and the baseline procedures on Day 0 (i.e., prior to the administration of the first dose of study drugs). Any untoward medical occurrence that initiated or worsened after completion of the initial screening visit procedures and before administration of the first dose of study drugs was to be recorded as a PTAE. Subjects were to be instructed to return to the clinic in 9 to 13 days.

Final Screening Visit (Day -1) Subjects were to return to the clinic after 9 to 13 days of washout for their final screening visit (Day -1). They were to undergo the following procedures: solicit for history of PTAEs since the previous visit and record medications taken since prior visit. Those who continued to meet eligibility criteria were to be given an ABPM, instructed in its use, and have the positioning of their ABPM checked. They were to be instructed to wear it at all times for the next 25 hours and to return to the clinic the following day.

Study Day 0: When the subjects returned to clinic the following day, the ABPM was to be collected and the data contained therein downloaded and analysed. If subjects were found to be hypertensive, based upon their ABPM measurement, they were to undergo additional baseline procedures as described below. If the subject's BP was too elevated for them to continue safely in the study (i.e., $SBP_{24h} > 169$ mmHg or $DBP_{24h} > 110$ mmHg), the subject was not to be enrolled and they were to be instructed to resume taking their prescribed BP medication as directed by the study doctor or general practitioner. If the subject was found to be normotensive ($SBP_{day} \leq 135$ mmHg), the subject was not to be enrolled. The subject's primary care doctor was to be informed that he/she had been found not to be hypertensive. No subject was to be randomized until these baseline ABPM data were reviewed and it was documented that the subject met entry BP criteria.

Subjects who met the BP criteria ($SBP_{day} > 135$ and ≤ 169 mmHg and $DBP_{day} \leq 110$ mmHg) following completion of the 10 to 14 day washout period were to undergo the following additional baseline procedures: solicit for history of PTAEs since the previous visit, targeted physical examination, body weight in underwear and light gown, vital signs, orthostatic hypotension evaluation, serum chemistry, and record medications taken since last visit. Subjects that continued to meet all eligibility requirements were to be enrolled in the study and randomized 3:3:1 to one of three treatment arms. The subjects were then to be administered their first dose of study drugs in the clinic.

Monitoring for TEAEs was to begin immediately following administration of the first dose of study drugs and was to continue throughout the study. Any untoward medical occurrence that initiated or worsened after the first dose of study drugs and within 14 days of the last dose of study drugs was to be recorded as a TEAE. Subjects were to remain in the clinic under observation for one hour following their first dose and were to be solicited for TEAE history prior to leaving the clinic. Subjects were to be provided with sufficient study drugs for the remainder of the 2-week treatment period, and instructed to take the study drugs qd in the morning. Subjects were to be provided with a diary and instructed to record any concomitant medications taken and details of study drug administration. Subjects were to be instructed to return to clinic the morning of Day 6.

Study Day 6: Subjects were to return to clinic on the morning of Day 6 and were to be solicited for history of TEAEs since the previous visit. The study drug containers were to be collected and unused

study drug counted and recorded. The diary was to be reviewed for details of study drug administration and any concomitant medications taken since the previous visit. Subjects were to be given an ABPM, instructed in its use, and have the positioning of their ABPM checked. The subjects were then to be administered their Day 6 dose of study drugs, and instructed to wear the ABPM at all times for the next 25 hours. Subjects were to be given back their remaining study drug supply and diary, instructed to record any concomitant medications taken and details of study drug administration, and to return to clinic the following day.

Study Day 7: The Day 7 study drugs were to be self-administered at home within 24 hours \pm 1 hour from the Day 6 dose. Subjects were to return to clinic on the morning of Day 7 (after the home administration of study drugs). The diary was to be reviewed for any concomitant medications taken and for details of study drug administration since the previous visit. The study drug containers were to be collected and unused study drug counted and recorded. Subjects were to be solicited for history of TEAEs since the previous visit. A targeted physical examination was to be performed and body weight in underwear and light gown and vital signs were to be measured. An orthostatic hypotension test was to be performed. Subjects were to have BP as measured by the ABPM recorded and the ABPM collected. Subjects were to have blood collected for measurement of creatinine (and calculation of creatinine clearance) and electrolytes.

If the Investigator determined that it was safe for the subject to continue in the study, the subject was to have their remaining study drug supply returned to them, and instructed to take the study drugs at home on Days 8-12, between 0700 and 1000 hours, and preferably at approximately the same time each day. Subjects were to be given back their diary and instructed to record any concomitant medications taken and details of study drug administration, and instructed to return to the clinic in 6 days (on the morning of Day 13).

If the subject's BP was too elevated for them to continue safely in the study (i.e., SBP_{24h} > 169 mmHg or DBP_{24h} > 110 mmHg), blood was to be drawn for renal profile testing. The subject was to be instructed to cease taking study drugs, instructed to resume taking their prescribed BP medication as directed by the study doctor or general practitioner, given back their diary and instructed to record any concomitant medications taken between visits, and instructed to return to the clinic in 7 days (Day 14).

Study Day 13: Subjects were to return to clinic on the morning of Day 13 (except for those discontinued from study drug due to excessive hypertension or other safety reasons) and were to be solicited for history of TEAEs since the previous visit. The diary was to be reviewed for details of study drug administration and any concomitant medications taken since the previous visit. The study drug containers were to be collected and any unused study drug counted and recorded. Subjects were to be given an ABPM, instructed in its use, and have the positioning of their ABPM checked. The subjects were then to be administered their Day 13 dose of study drugs (final dose), and instructed to wear the ABPM at all times for the next 25 hours. Subjects were to be given back their diary and instructed to record any concomitant medications taken between visits, and instructed to return to clinic the following day.

Study Day 14: Subjects were to return to clinic on the morning of Day 14. The diary was to be reviewed for any concomitant medications taken since the previous visit. Subjects were to be solicited for history of TEAEs since the previous visit. A comprehensive physical examination was to be performed and body weight in underwear and light gown and vital signs were to be measured. BP as measured by the ABPM was to be recorded and the ABPM collected. An orthostatic hypotension evaluation was to be performed. The following additional evaluations were to be performed: 12-lead ECG, hematology, serum chemistry, urinalysis, and urine pregnancy test for WCBP.

In addition, subjects were to have a blood sample collected 24 hours \pm 1 hour post-dose for measurement of amlodipine concentrations. Only subjects enrolled at Investigational Sites that had UV-shielded lights were to participate in the PK blood collections. Due to the design of the trial (randomized, double-blind, placebo-controlled), this blood sample was to be collected and analyzed for all participating subjects, regardless of whether they were in a treatment arm that received amlodipine.

Following the Day 14 evaluations, the subjects were to be instructed to resume taking their prescribed BP medication as directed by the study doctor or general practitioner, given back their diary and instructed to record any concomitant medications taken between visits, and instructed to return to the clinic in 14 days (Day 28).

Study Day 28: Subjects were to return to clinic on Day 28 for their final study visit (follow-up visit). The diary was to be reviewed for any concomitant medications taken since the prior visit. Subjects were to be solicited for history of TEAEs since the previous visit. A targeted physical examination was to be performed and vital signs were to be measured. For subjects whose study drugs were discontinued at Day 7, this follow-up visit was still occur on Day 28 (i.e., these subjects were to return to the clinic for both the Day 14 and Day 28 visits).

The schedule of events is provided in the table below.

| Event | Screening | | Baseline/ 1 st Dose | Remainder of Treatment Period | | | Follow-up | |
|--|----------------------------|-----------------------------|-----------------------------------|-------------------------------|------------------|--------|-----------------------|-----------------------|
| | Initial Screening Visit | Final Screening Visit | Day 0 | Day 6 | Day 7 | Day 13 | Day 14 ^(a) | Day 28 ^(a) |
| | Day -14 to -10 | Day -1 | | | | | | |
| Informed consent ^(b) | X | | | | | | | |
| Record demographic data | X | | | | | | | |
| Complete medical history | X | | | | | | | |
| Monitor for pretreatment adverse events (PTAEs) ^(k) | X | X | X | | | | | |
| Record prior medications | X | X | X | | | | | |
| Record concomitant medications (CM) | | | X | X | X | X | X | X |
| Height and BMI | X | | | | | | | |
| Body weight while only wearing underwear and a light gown | X | | X | | X | | X | |
| Comprehensive physical examination ^(c) | X | | | | | | X | |
| Targeted physical examination ^(d) | | | X | | X | | | X |
| Vital Signs ^(e) | X ^(e) | | X | | X | | X | X |
| Provide ABPM and instruct on use | | X | | X | | X | | |
| 25-hour monitoring of BP via ABPM ^(f) | | X | | X | | X | | |
| Orthostatic hypotension evaluation | | | X | | X | | X | |
| 12-lead ECG | X | | | | | | X | |
| Hematology ^(g) | X | | | | | | X | |
| Serum chemistry ^(g) | X | | X | | X ^(g) | | X | |
| Serum pregnancy test ^(h) | X | | | | | | | |
| Urine pregnancy test ^(h) | | | | | | | X | |

| Event | Screening | | Baseline/ 1 st Dose | Remainder of Treatment Period | | | Follow-up | |
|--|----------------------------|-----------------------------|-----------------------------------|-------------------------------|-------|--------|-----------------------|-----------------------|
| | Initial Screening Visit | Final Screening Visit | Day 0 | Day 6 | Day 7 | Day 13 | Day 14 ^(a) | Day 28 ^(a) |
| | Day -14 to -10 | Day -1 | | | | | | |
| Urinalysis ^(g) | X | | | | | | X | |
| Urine drug screen ^(g) | X | | | | | | | |
| Review inclusion/exclusion criteria | X | X | X | | | | | |
| Randomization ⁽ⁱ⁾ | | | X | | | | | |
| Administer study drug in clinic ⁽ⁱ⁾ | | | X | X | | X | | |
| Provide diary to record CMs and study drug details | | | X | | | | | |
| Review diary | | | | X | X | X | X | X |
| Collect study drug containers/capsule count | | | | X | X | X | | |
| Monitor for treatment emergent adverse events (TEAEs) ^(k) | | | X | X | X | X | X | X |
| Blood collection for PK ^(l) | | | | | | | X | |

- a. If a subject was discontinued from study drug early, all study evaluations described for Day 14 and Day 28 were to be performed if feasible. Study drug-related AEs (adverse reaction or suspected adverse reaction per the definitions in Section 8.1.3 of the protocol) were to be followed until resolution or stabilization.
- b. ICF must have been signed prior to performing any other screening evaluations
- c. Comprehensive physical examination was to include the following organ or body system assessments: skin; head, eyes, ears, nose, and throat; thyroid; lungs; cardiovascular; abdomen (liver, spleen); lymph nodes; and extremities, as well as an abbreviated neurological exam
- d. Targeted physical examination were to specifically target the cardiovascular system and were to include vital signs, plus an examination of the extremities to check for the presence of edema, as well as an examination to document any other evidence of a cardiovascular problem. Any areas of concern from the medical history or noted on the prior physical examination or indicated by subject symptoms or other findings as determined by the Investigator or designee may also have been examined.
- e. BP, pulse rate, respiration rate, and oral body temperature. At the Initial Screening Visit, the arm with the higher average clinical visit systolic BP was to be determined and used for all further BP measurements including ABPM measurements (see Section 8.3 of the protocol).

- f. BP was to be continually recorded with an ABPM on one to three 25-hour periods during the trial: Day -1 to Day 0, Day 6 to Day 7, and Day 13 to Day 14 (see Section 7.1 of the protocol for further detail)
- g. See Appendix B of the protocol for a list of the specific hematology, serum chemistry, urinalysis, and drug tests. The serum chemistry tests at Day 7 was to be limited to creatinine (and calculation of creatinine clearance) and electrolytes (sodium, bicarbonate, calcium, chloride, phosphorous, and potassium), rather than the full panel listed in Appendix B.
- h. Only for WCBP
- i. Only after all other baseline procedures have been completed and the subject's eligibility was confirmed. Subjects were to be randomized 3:3:1 to one of three treatment arms (see Section 5.2 of the protocol)
- j. Subjects were to take study drug by mouth qd for 14 days (Days 0-13) for a total of 14 doses. With the exception of Days 0, 6 and 13, when study drug intake was at the time of clinic visit, the subjects were to be instructed to take the study drugs between 0700 and 1000 hours, and preferably at approximately the same time each day. At each dose, subjects were to take one capsule from each of the two containers (OE amlodipine besylate tablet or matched placebo for the OE amlodipine besylate tablet and OE celecoxib capsule or matched placebo for OE celecoxib capsule). The first dose of study drug (morning dose on Day 0) and the Day 6 and Day 13 doses were to be taken in the clinic, and all remaining doses were to be self-administered at home. Subjects were to be provided with a diary to record the details of study drug administration.
- k. Monitoring for PTAEs was to begin upon completion of the initial screening visit procedures and was to continue through the 9 to 13 days of washout, the final screening visit on Day -1, and the baseline procedures on Day 0 (i.e., prior to the administration of the first dose of study drugs). Monitoring for TEAEs was to begin immediately following administration of the first dose of study drugs and was to continue throughout the study. Subjects were to be solicited for PTAE history at Day -1 and Day 0 (pre-dose). Subjects were to be solicited for TEAE history prior to leaving the clinic on Day 0 and on Days 6, 7, 13, 14, and 28. In order to avoid bias in eliciting AEs, subjects were to be asked general, non-leading questions such as "How are you feeling?"
- l. For PK analysis, blood samples were to be obtained at 24 hours \pm 1 hour post-dose for measurement of amlodipine concentrations. Only subjects enrolled at Investigational Sites that had UV-shielded lights were to participate in the PK blood collection. Due to the design of the trial (randomized, double-blind, placebo-controlled), this blood sample was to be collected and analyzed for all participating subjects, regardless of whether they were in a treatment arm that received amlodipine.

3.1. Sample Size

The sample size was based on findings of the KIT-302-03-01 study, and on the hypothesis that the mean reduction in SBP_{day} from baseline to Day 14 of subjects treated with amlodipine tablets (10 mg) and celecoxib capsules (200 mg) given together (arm 1) minus half the mean reduction in SBP_{day} from Baseline to Day 14 of subjects treated with amlodipine tablets (10 mg) given alone (with matched celecoxib placebo) (arm 2) is at least 0.

Sample size was based on the formula

$$n = \left\lceil 2 \left(\frac{Z_{1-\alpha} + Z_{1-\beta}}{d} \right)^2 s^2 \right\rceil$$

Where:

s is the SD (8.7)

d is the anticipated mean difference (6.2)

α is the one-sided level of significance (0.025)

$1-\beta$ is the power, one-sided (80%)

$\lceil \rceil$ is the ceiling function

The margin was based on a mean reduction of 8.8 mmHg in SBP_{day} for the amlodipine + placebo arm and a mean reduction of 10.6 mmHg for the amlodipine + celecoxib arm as seen in the previous study, KIT-302-03-01. To ensure that at least half the effect is maintained, a value of $10.6 - 0.5(8.8) = 6.2$ mmHg should be set for d .

The SD was based on an 8.1 mmHg SD for the amlodipine + placebo arm and a 9.2 mmHg SD for the amlodipine + celecoxib arm in the previous study (KIT-302-03-01). The pooled SD for the power and sample size justification is 8.7 mmHg.

The final sample size was rounded up to allow for a loss to follow-up. The study selected a round number at least 10% larger than the number necessary to protect against potential subjects not fully participating in the entire trial.

Approximately 105 subjects were to be randomized. Therefore, a sufficient number of subjects were to be screened so as to achieve approximately 105 subjects entering the randomization phase (starting at Day 0).

3.2. Randomization

This is a randomized, double blind, placebo controlled study. Per protocol, approximately 105 subjects were to be randomized 3:3:1 to one of three treatment arms:

1. OE 10 mg amlodipine besylate tablet + OE 200 mg celecoxib capsule;
2. OE 10 mg amlodipine besylate tablet + matched placebo for OE celecoxib capsule;
3. Matched placebo for OE amlodipine tablet + matched placebo for OE celecoxib capsule.

The description that follows is based on the final protocol, as well as “Note to File - Explanation of 6:6:1 Randomization” (dated March 30, 2018), a copy of which is available in the Trial Master File. Randomization was to take place on Day 0 when the subject returned to clinic and was found to have

hypertension based upon the ABPM recordings and continued to meet eligibility criteria following baseline procedures. Once the 105th subject was randomized to treatment (Day 0), any subject that was currently participating in the washout period was to be allowed to complete the washout period and if found eligible was to be enrolled into the trial. These subjects were to continue to be randomized 3:3:1 as noted above. No further subjects were to be brought in for the Initial Screening Visit once the 105th subject was randomized.

A computer-generated randomization schedule was used for assigning the sequence in which subjects were assigned to treatment arms. Generation of the randomization schedule and shipment of blinded study drug patient kits to the Investigational Sites were performed by PCI Pharma Services, Western Avenue, Bridgend Industrial Estate, Bridgend, CF31 3TY, United Kingdom (PCI Bridgend). PCI Bridgend used PRISM ClinTrial labeling software to generate the randomization codes. The randomization codes were prepared in blocks of 7 to ensure the appropriate number of subjects per treatment arm (i.e., 3 + 3 + 1). The software generated unique 3-digit patient kit numbers in an ascending, consecutive, numerical sequence from 501 to 997 (71 blocks).

Labeling of the patient kits was performed by PCI Pharma Services, Inc., 4545 Assembly Drive, Rockford, IL 61109 US (PCI Rockford). As the trial only called for approximately 105 randomized subjects, not all of the 497 randomization codes were used for labeling. Further, due to how PCI Rockford ran the labeling, the resulting kits available for distribution had gaps in the sequence. Specifically, 1) the labeling was done in multiple runs, 2) each run started with the highest number of the planned batch and ran backwards to the lowest planned number (e.g., if 1-100 kit numbers were to be labeled in a run, PCI started with kit number 100 and worked back to 1), and 3) extra labels ordered to avoid having to reorder during the run if a label was damaged were scrapped if not used (e.g., if 100 kits were to be labeled, 120 numbers would be ordered, and any of the additional 20 numbers that were not used during the run were no longer available for labeling).

The randomization code was issued to William Berlin, PhD., Berlin Pharmaceutical Consulting, LLC, Rockville, MD, US who was unblinded to the study. William provided the contract research organization (CRO) responsible for project management and study monitoring (Java Clinical Research Ltd, Denshaw House, 120-121 Baggot Street Lower, Dublin 2, Ireland) the list of available kit numbers to enable them to request the next set of kits in the sequence for dispatch; however, the CRO remained blinded to the study.

Initial shipments of study drug to individual Investigational Sites were to include 5 patient kits with sequential randomization numbers. Due to the labeling issue noted above, the sequential numbers were not necessarily consecutive. Additionally, the initial shipments for four of the Investigational Sites included more than 5 kits to meet the anticipated higher enrollment rates at these sites (Site 301 - Queen Mary School of Medicine & Dentistry: 10 kits, Site 302 – Celerion, Belfast: 14 kits, Site 303: Rowden Surgery: 7 kits, and Site 304 - Medicines Evaluation Unit: 21 kits). The kit numbers for these larger shipments were also sequential, but again, not necessarily consecutive.

As subjects were enrolled, the Investigator was to take the next sequential kit number in the block provided and assign it to the subject. Due to the issues with labeling noted above (resulting in gaps in available kit numbers), the kit numbers were assigned sequentially, but were not necessarily consecutive. Further, due to the variation in the number of kits initially sent to each site (ranging from 5 to 21), the initial shipment may have included less than a full block or up to two full blocks and two partial blocks.

The Investigational sites were to be re-supplied in the same fashion (i.e., 5 patient kits); however, to accommodate differences in enrollment rate, the number of kits in the resupply shipments ranged from 2 to 10, with each shipment containing sequential randomization numbers. The Investigator was to take the next sequential kit number in the resupply shipment and assign it to the subject. The

sequential numbers were not necessarily consecutive due to the labeling issue noted above. At the end of the study, any unused kits were returned to the distributor.

Subjects were to be randomized 3:3:1, however, the final overall randomization was 6:6:1. The difference is attributed to 1) the labeling issues noted above that led to gaps in the available kit numbers, 2) the distribution of the kits in sequential order from lowest to highest available kit number, 3) the number of kits shipped initially and as re-supply, and 4) only using some of the kits shipped as fewer subjects were enrolled than kits shipped.

As both the primary and secondary efficacy endpoints are based on comparisons of treatment arms 1 and 2, and the ratio of these two arms are similar under a 3:3:1 and a 6:6:1 randomization, this difference from the planned randomization is not anticipated to impact the trial outcomes. A site-specific analysis of the primary endpoint will be done (see Section 1.3.13) to evaluate for any impact that variation in the randomization ratio across sites may have on the outcome.

4. Analysis Sets

4.1. Study Populations

There are seven populations for this study, the ITT, mITT, PP, Safety, PK, Randomized, and Overall Trial populations.

ITT population: The definition of the ITT population as stated in the protocol was at risk of losing randomized subjects and will be changed to remain faithful to the ITT principal. The ITT population will include all randomized subjects with a valid ABPM measurement at baseline (Day -1 to Day 0) according to the definition of validity described in Section 1.3.1. The protocol definition required valid Baseline and valid follow-up ABPM measurements, either Day 6 or Day 13. This definition will instead be used for a mITT population (see below), and the mITT population will be used for sensitivity analyses as described in Section 1.3.3.2.

In the event there are no Day 6 to Day 7 and no Day 13 to Day 14, baseline will be carried forward.

mITT population: The definition of the mITT population will follow the definition of the ITT population in the protocol with regards to the number of ABPMs required (although based on the revised ABPM validity definition in Section 1.3.1). Thus, the mITT population will be comprised of randomized subjects with at least a valid baseline (Day -1 to Day 0) ABPM measurement and either

- a. A valid final (Day 13 to Day 14) ABPM measurement, where a subject completes the treatment program.
- or
- b. A valid Day 6 to Day 7 ABPM measurement, where a subject is withdrawn from the treatment program at that point because of an $SBP_{24h} > 169$ mmHg and/or a $DBP_{24h} > 110$ mmHg, or if they are withdrawn for any other reason.

Subjects that do not have the two paired valid ABPM measurements, as required (baseline and final, for those who complete the treatment program, or baseline and Day 6 to Day 7, for those withdrawn from the study), will not be included. In the event there is no Day 13 to Day 14 ABPM measurement, the Day 6 to Day 7 ABPM measurement will be carried forward.

PP population: The PP population will be comprised of randomized subjects with at least a valid baseline (Day -1 to Day 0) ABPM measurement and also a valid final (Day 13 to Day 14) ABPM measurement.

Dropouts and subjects who had major violations of the protocol will be excluded. Major protocol violations will include missing more than 25% of scheduled doses of study drugs, and taking prohibited medications including any NSAIDs or calcium channel blockers (other than the study drugs).

All randomized subjects should receive their initial dose of study drugs in the clinic immediately following randomization.

Safety population: All randomized subjects who received at least one dose of study drug will be included in the safety population. Analysis of safety variables, demographic and screening/baseline characteristics, past and concomitant diseases, previous and concomitant medications, and treatment compliance and extent of exposure will be performed on the safety population.

PK population: All subjects that were enrolled at an Investigational Site that had UV-shielded lights **and** who had a blood sample drawn on Day 14, 24 hours \pm 1 hour after receiving the final dose of study drugs, for the measurement of plasma amlodipine concentration. This population will be used to produce the summary tabulation, t-test analysis, and box-plot analysis of the non-transformed plasma amlodipine concentration values, as well as the summary tabulation and t-test analysis of the log-transformed values.

Randomized population: All randomized subjects. The Randomized population will be used to produce all listings, except screening failures and the listing of plasma amlodipine concentrations. The screening failures listing will use the Overall Trial population and the listing of plasma amlodipine concentrations will use all subjects that were enrolled at an Investigational Site that had UV-shielded lights. The Randomized population will also be used to produce a summary tabulation of subjects who completed the study and who discontinued the study after randomization, and the primary reason for discontinuation. The Randomized population will also be used to produce a summary tabulation of the number of subjects in the randomized population, the ITT population, the mITT population, the PP population, the safety population, and the PK population.

Overall Trial population: All patients screened. This population will be used to produce a listing of screening failures and a tabular summary of the number of patients at Initial Screening Visit, at Final Screening Visit, at Baseline, randomized, and at each remaining study visit.

4.2. Misallocations

In case an error occurs in treatment allocation, the following rule will be followed: if a patient was randomized but received the incorrect study drug, he/she will be reported under his/her randomized treatment group for all analyses performed on the randomized, ITT, mITT, and PP populations, but he/she will be reported under the treatment actually received for all analyses performed on the safety and PK populations.

4.3. Protocol Deviations

All the protocol violations will be discussed case by case before unblinding of the treatment code with the clinical team during the blind review of the data and described in the Data Review Report.

5. Definitions and Data Conventions

This section contains definitions and conventions that will be used for analysis.

General, demographic and baseline characteristics

Age and BMI (kg/m²)

Age and BMI will not be recalculated. The values automatically derived in the CRF will be used in the analysis.

Past disease and concomitant disease

Past disease: A medical condition that initiated and ended prior to the Initial Screening Visit. Thus, any disease/history listed on the “Cardiovascular History” or “Medical History and/or Concomitant Diseases” CRFs that has a stop date that is prior to the Initial Screening Visit date, if a stop date is available, and that has “no” checked for “Ongoing”. Any surgery listed on the “Surgical History” CRF that has a date that is prior to the Initial Screening Visit date is considered as a past disease.

Concomitant disease: A medical condition that is ongoing at the Initial Screening Visit. Thus, any disease/history listed on the “Cardiovascular History” or “Medical History and/or Concomitant Diseases” CRFs that has no stop date entered and that has “yes” checked for “Ongoing”. Any surgery listed on the “Surgical History” CRF that has a date equal to the Initial Screening Visit date is considered as a concomitant disease. Any disease that initiates after completion of the Initial Screening Visit procedures and before administration of the first dose of study drugs on Day 0 will be recorded as a PTAE (and will not be considered as a concomitant disease for the purpose of the concomitant disease listing and tabulation).

Previous, concomitant, posterior, and unclassified medications

Previous medication: Medications with a start date < date of first randomized study drug intake and a stop date < date of first randomized study drug intake.

Concomitant medication: Medications (other than the study drugs) with either:

- a) a **start date** \geq date of first randomized study drug intake and \leq date of final study visit assessment; or
- b) a **start date** < date of first randomized study drug intake and a **stop date** \geq date of first randomized study drug intake

Posterior medication: Medications with a start date > date of final study visit assessment.

For the medications listing, medications will be classified as either Type 1 (previous medication), Type 2 (concomitant medication), Type 3 (posterior medication), or Type 4 (unknown). Tabular summaries will be prepared for each classification (i.e., previous medications, concomitant medications, posterior medications, and medications that could not be classified as previous, concomitant, or posterior due to unknown or partial start or stop dates). If there are no Type 4 medications, then the corresponding tabular summary will not be produced.

The table that follows provides the imputation method to be used for assigning medication classification, including in instances when all or part of a start or stop date is missing.

| Information Available for Start Date | Information Available for Stop Date | Type |
|--|--|------|
| Full start date available and: | | |
| Full end date available and: | | |
| <date of 1 st dose | <date of 1 st dose | 1 |
| <date of 1 st dose | >= date of 1 st dose | 2 |
| >= date of 1 st dose & <= date of final assessment | after start date | 2 |
| > date of final assessment | > date of final assessment | 3 |
| Full start date available and: | | |
| Partial or Unknown Stop Date | | |
| <date of 1 st dose | Nothing (D, M, & Y unknown) | 4 |
| = date of 1 st dose | Nothing (D, M, or Y unknown) | 2 |
| > date of 1 st dose, but ≤ date of final assessment | Nothing (D, M, or Y unknown) | 2 |
| > date of final assessment | Nothing (D, M, or Y unknown) | 3 |
| Partial or Unknown Start Date | | |
| Full stop date available and: | | |
| Only Y known | = date of 1 st dose | 2 |
| Only M & Y known | | 2 |
| Only Y known | > date of 1 st dose, but ≤ date of final assessment | 2 |
| Only M & Y known | | 2 |
| Only Y known | > date of final assessment | |
| If < Y of 1 st dose | | 2 |
| If = Y of 1 st dose | | 4 |
| If > Y of 1 st dose | | 4 |
| Only M & Y known | | |
| If < M & Y of 1 st dose | | 2 |
| If = M & Y of 1 st dose | | 4 |
| If > M & Y of 1 st dose | | 4 |
| Only Y known | < date of 1 st dose | 1 |
| Only M & Y known | < date of 1 st dose | 1 |

| Information Available for Start Date | Information Available for Stop Date | Type |
|--|-------------------------------------|------|
| Partial or Unknown Start Date | Partial or Unknown Stop Date | |
| Nothing (D, M, or Y unknown) | Nothing (D, M, or Y unknown) | 4 |
| Only Y known | | |
| If > Y of final assessment | Nothing (D, M, or Y unknown) | 3 |
| If < or = Y of 1 st dose | Nothing (D, M, or Y unknown) | 4 |
| Only M & Y known | | |
| If <= M & Y of 1 st dose | Nothing (D, M, or Y unknown) | 4 |
| If > M & Y of final assessment | Nothing (D, M, or Y unknown) | 3 |
| If > M & Y of 1 st dose and = M & Y of final assessment | Nothing (D, M, or Y unknown) | 4 |

D = day, M = month, Type 1 = previous medication, Type 2 = concomitant medication, Type 3 = posterior medication, Type 4 = unknown, Y = year

Study drug intake

Date of first randomized study drug intake is the actual date of study drug administration at Day 0 reported in the “Study Drug Administration Recorded in the Diary Card” CRF.

However, any discrepancy between the date of Day 0 reported elsewhere in the CRF and the date of administration at Day 0 reported in the “Study Drug Administration Recorded in the Diary Card” CRF will be evaluated during the Data Review Meeting.

Date of last randomized study drug intake is the date of last study drug intake recorded in the “Study Termination” CRF. If this date is missing, the last date of administration reported in the “Study Drug Administration Recorded in the Diary Card” CRF will be considered.

However, any discrepancy between last date of administration reported in the “Study Drug Administration Recorded in the Diary Card” CRF and the date of last study drug intake recorded in the “Study Termination” CRF will be evaluated during the Data Review Meeting.

Treatment Compliance & Extent of Exposure

Each of the OE drug products was supplied in a separate container. At each dose, subjects took one capsule from each of the two containers (i.e., OE 10 mg amlodipine tablet or matched placebo for the OE amlodipine tablet and OE 200 mg celecoxib capsule or matched placebo for the OE celecoxib capsule).

So as to aid in identifying the study drugs, orange capsules were used to over-encapsulate the amlodipine tablets and for the matched placebo for the OE amlodipine tablets and white capsules were used to over-encapsulate the celecoxib capsules and for the matched placebo for the OE celecoxib capsule.

Each study drug was supplied in 15-count high-density polyethylene bottles with child resistant closures. The double-blind labeling kit (carton) contained one 15-count bottle of OE 10 mg amlodipine tablet or matched placebo for the OE amlodipine tablet and one 15-count bottle of OE 200 mg celecoxib capsule or matched placebo for the OE celecoxib capsule.

All drugs were to be administered orally qd for 14 days (Days 0-13) for a total of 14 doses. Thus, due to the 15-count packaging, the subjects were dispensed one extra dose of each drug (one extra orange capsule and one extra white capsule) that was to be returned at the end of the treatment period.

The first dose was to be administered in the clinic on Day 0, as were the doses to be taken on Day 6 and Day 13. The remainder of the doses were to be self-administered at home.

With the exception of Day 0, when study drug intake was after determination of eligibility (and at least 25 hours after the Day -1 ABPM was initiated), Days 6 and 13, when study drug intake was to be at the time of fitting the ABPM (following fitting) and Day 7, when study drug intake was to be $24 \text{ h} \pm 1 \text{ h}$ after the Day 6 dose, the subjects were to be instructed to take the study drugs between 07:00 and 10:00, and preferably at approximately the same time each day.

Subjects were to be provided with a diary to record details of study drug administration for each dose [date, time, and number of orange and white capsules taken], and were to be instructed to return the completed diary at the Day 6, Day 7, and Day 13 clinic visits. Subjects were also to be instructed to bring both of their study drug containers (orange and white capsules) back to the clinic at Day 6, Day 7 and Day 13.

The Investigational Site personnel were to collect the study drug containers and count and record unused study drug. Subjects were to return 9 orange capsules and 9 white capsules on Day 6 (and after taking the Day 6 dose in the clinic, be left with 8 of each colored capsule to take home with them). Subjects were to return 7 orange capsules and 7 white capsules on Day 7 (having taken the Day 7 dose at home before coming to the clinic). Subjects were to return 2 orange capsules and 2 white capsules on Day 13 (and after taking the Day 13 dose in the clinic, be left with 1 of each color of capsule that would not be taken, but returned to the pharmacy).

Further, the Investigational Site personnel were to collect the diaries and review and record the study drug administration details in the CRF. Doses taken in the clinic were to be witnessed by the Investigational Site personnel and were to be recorded by the Investigational Site personnel in the diary and CRF.

The primary analysis of treatment compliance and extent of exposure will be based on the data entered in the "Study Drug Administration Recorded in the Diary Card", and will be performed for the Safety population as described below. The capsule count data will be provided in listing format only.

The summary tabulation of treatment compliance and extent of exposure will include the following:

1. Total number of orange capsules (OE 10 mg amlodipine besylate tablets or matched placebo), summarized by descriptive statistics (n, mean, SD, median, and range) for each treatment arm and overall
2. Total number of white capsules (OE 200 mg celecoxib capsules or matched placebo), summarized by descriptive statistics (n, mean, SD, median, and range) for each treatment arm and overall
3. Percentage of orange capsule planned dose taken, calculated by dividing the total number of orange capsules taken (derived from the "Study Drug Administration Recorded in the Diary Card" CRF) by 14 and multiplying by 100, and summarized by descriptive statistics (n, mean, SD, median, and range) for each treatment arm and overall

4. Percentage of white capsule planned dose taken, calculated by dividing the total number of white capsules taken (derived from the “Study Drug Administration Recorded in the Diary Card” CRF) by 14 and multiplying by 100, and summarized by descriptive statistics (n, mean, SD, median, and range) for each treatment arm and overall
5. Percentage and number of subjects in each of three compliance categories for orange capsules, by treatment arm and overall. The compliance categories for orange capsules will be:
 - a. <75% (i.e., all subjects who had a percentage of orange capsule planned dose taken less than 75%)
 - b. $75\% \leq X < 100\%$ (i.e., all subjects who had a percentage of orange capsule planned dose taken greater than or equal to 75% and less than 100%)
 - c. 100% (i.e., all subjects who had a percentage of orange capsule planned dose taken of 100%)
6. Percentage and number of subjects in each of three compliance categories for white capsules, by treatment arm and overall. The compliance categories for white capsules will be:
 - a. <75% (i.e., all subjects who had a percentage of white capsule planned dose taken less than 75%)
 - b. $75\% \leq X < 100\%$ (i.e., all subjects who had a percentage of white capsule planned dose taken greater than or equal to 75% and less than 100%)
 - c. 100% (i.e., all subjects who had a percentage of white capsule planned dose taken of 100%)
7. Total treatment duration in days, calculated as the date of last study drug intake minus the date of first study drug intake + 1, and summarized by descriptive statistics (n, mean, SD, median, and range) for each treatment arm and overall.

6. Efficacy Variables

6.1. Primary Efficacy Variable

SBP_{day}

The primary efficacy variable will be SBP_{day}. Appendix A of this SAP outlines the methodology for obtaining this variable.

6.2. Secondary Efficacy Variables

Body Weight

The measurement of the change in body weight from baseline to the end of treatment will serve as an indirect measure of renal function and is the first secondary efficacy endpoint analyzed in the serial gatekeeping strategy. Body weight will be measured while the subject is wearing only underwear and a light gown.

SBP_{24h} and DBP_{24hr}

The next secondary efficacy endpoints (after change in body weight) used in the serial gatekeeping strategy are the change in SBP_{24h} from the baseline to the end of treatment and the change in DBP_{24h} from baseline to the end of treatment, respectively. Appendix A of this SAP outlines the methodology for obtaining these variables.

For efficacy analyses, the validity of ABPM measurements will be based on valid daytime measurements. The impact of defining valid SBP_{24h} and DBP_{24h} measurements based on valid daytime readings is that some invalid measurements with respect to the 24-hour period (i.e., not meeting criterion d or e listed in Section 1.3.1) will remain in the analysis of the 24-hour variables. Sensitivity analyses excluding measurements that had an entry of valid for day validity and an entry of invalid for night or 24h validity will be conducted to verify that the inclusion of the invalid measurements does not impact the secondary efficacy conclusions. Details of the Sensitivity analyses are described in Section 7.10.

Renal function

The final secondary efficacy endpoint in the serial gatekeeping strategy is the change in creatinine clearance from baseline to end of treatment. Creatinine clearance will be estimated by the Cockcroft-Gault equation as follows:

$$\text{Estimated creatinine clearance} = \frac{(140 - \text{age}) \times \text{body weight (kg)}}{72 \times P_{Cr} \left(\frac{\text{mg}}{\text{dL}} \right)}$$

Note: multiply by 0.85 for women

6.3. Exploratory and Other Efficacy Variables

Exploratory Efficacy Variables

Exploratory efficacy variables will include DBP_{day}, SBP_{night}, and DBP_{night}, and two-sample t-tests to test one-side hypotheses of superiority for pairwise comparisons between treatment arms 1 and 2, 1 and 3, and 2 and 3 will be performed for each. Further, SBP_{day}, SBP_{24h}, and DBP_{24h} will serve as exploratory efficacy variables for the two-sample t-tests to test one-side hypotheses of superiority for pairwise comparisons between treatment arms 1 and 3 and 2 and 3 (the comparison of treatment arms 1 and 2 for these endpoints are covered separately under the respective primary and secondary efficacy analyses). Appendix A of this SAP outlines the methodology for obtaining these variables.

For the efficacy analyses, the validity of ABPM measurements will be based on valid daytime measurements. The impact of defining valid SBP_{night} and DBP_{night} measurements based on valid daytime readings is that some invalid night-time readings (i.e., not meeting criterion d listed in Section 1.3.1) will remain in the analysis of night-time variables. Sensitivity analyses excluding measurements that had an entry of valid for day validity and an entry of invalid for night validity will be conducted to verify that inclusion of the invalid measurements does not impact the exploratory efficacy conclusions. Details of the Sensitivity analyses are described in Section 7.10. See Section 6.2 regarding the impact of defining valid SBP_{24h} and DBP_{24h} measurements based on valid daytime readings.

SBP and DBP at Amlodipine Peak and Trough

Other efficacy variables will include SBP and DBP at the expected peak amlodipine concentration and at the trough amlodipine concentration at Day 6 and Day 13, and the difference of the values between Day 6 and Day 13. The peak and trough values will be taken from the ABPM measurements. See Section 7.10 for further definition of the peak and trough values.

6.4. Safety Variables

Safety will be assessed primarily based on reported TEAEs. Clinically significant clinical laboratory abnormalities will be reported as AEs (i.e., as either PTAEs or TEAEs, depending on when they initiate or worsen).

PTAE

Any untoward medical occurrence that initiates or worsens after completion of the Initial Screening Visit procedures and before administration of the first dose of study drugs will be recorded as a PTAE.

TEAE

Any untoward medical occurrence that initiates or worsens after the first dose of study drugs and within 14 days of the last dose of study drugs will be recorded as a TEAE.

In case of missing or incomplete dates and times not allowing a direct allocation to either of the two categories of AEs, a worst-case allocation will be done according to the available parts of the onset and the end dates. The AE will be allocated to the first category allowed by the available data, according to the following order:

- TEAE
- PTAE.

SAE

A SAE is any untoward medical occurrence that results in death, is life-threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, is a congenital anomaly/birth defect, or is an important medical event that, based upon appropriate medical judgement, may jeopardize the subject and may require medical or surgical intervention to prevent one of the former outcomes (i.e., AE with seriousness not equal to '0' on AE CRF).

ADR

An ADR is an AE with relatedness to Study Drug judged as an "Adverse Reaction" (i.e., an AE that is caused by the study drug) or a "Suspected Adverse Reaction" (i.e., an AE for which there is a reasonable possibility that the study drug caused the AE) [i.e., an AE with relatedness to study drug not equal to 'unrelated' on AE CRF].

Oedema events

An oedema event is any TEAE with a PT of oedema, oedema peripheral, peripheral swelling, swelling, or joint swelling.

Other PTs of interest

Other PTs of interest will be defined as any TEAE with a PT of orthostatic hypotension, fall, dizziness, dizziness postural, or vertigo.

UAE

Per the protocol, an UAE is one for which the nature or severity of the event is not consistent with the applicable study drug information [i.e., the most current version of the Investigator's Brochure (IB), the current product labeling for amlodipine tablets, and the current product labeling for celecoxib capsules] or listed in the protocol (as provided below).

This study was to enroll older subjects with existing hypertension. To that end, PTAEs and TEAEs could be expected due to the subjects' age and underlying conditions. These include: hypertension, hypertensive crisis, myocardial infarction, congestive heart failure, stroke both hemorrhagic and ischemic, any adult forms of cancer, and gastrointestinal ulcerations with complications including hemorrhage and perforation.

By definition, PTAEs initiate prior to administration of the first dose of study drugs, and thus a comparison against study drug specific risk information is inappropriate for determining expectedness

of PTAEs. Thus, only AEs that can be expected due to subject age and underlying conditions are relevant for the expectedness determination for PTAEs.

TEAE leading to discontinuation

A TEAE leading to discontinuation is a TEAE with ‘the Primary Reason for discontinuation’ equal to “Treatment Emergent Adverse Event” on the Study Termination CRF.

PTAE leading to withdrawal

A PTAE leading to withdrawal is a PTAE listed as the reason for the subject not being randomized to treatment on the “Study Termination” CRF.

AE leading to death

An AE leading to death is an AE with outcome equal to “Fatal” on AE CRF.

Amlodipine dose and celecoxib dose

The following variables will be derived for the logistic models:

| Treatment group | Amlodipine dose | Celecoxib dose |
|------------------------|------------------------|-----------------------|
| Amlodipine + Celecoxib | 10 mg | 200 mg |
| Amlodipine + Placebo | 10 mg | 0 mg |
| Placebo + Placebo | 0 mg | 0 mg |

Count of AEs

Two AEs with the same PT and classified in the same category (PTAE or TEAE) that do not overlap in date of occurrence will be considered as two different events when calculating the “number of events” in the tables.

Secondary safety variables will include physical examination, body weight, vital signs, orthostatic hypotension evaluations, ECG, hematology, serum chemistry, and urinalysis.

Physical examination

The protocol-specified organ or body systems for the comprehensive physical examination will be used in the summary tabulation [i.e., skin; head, eyes, nose and throat; thyroid; lungs; cardiovascular; abdomen (liver, spleen), lymph nodes, extremities, and neurological (abbreviated exam)]. The targeted physical examination findings will only be provided as a listing.

Body weight

Body weight will serve a dual function as both a secondary efficacy endpoint (see Section 6.2) and as a safety endpoint. For the latter, the body weight and change in body weight for the Safety population will be used for analysis.

Vital signs

Clinic visit resting systolic and diastolic blood pressure, pulse rate, respiration rate, and oral body temperature will be used for analysis.

For resting systolic and diastolic blood pressures, the Average values of 3 recordings reported in the CRF (derived) will be used in the analysis. The recordings 1, 2 and 3 will be only listed.

The continuous recording of BP by ABPM will serve a dual function as both the official BP values for all efficacy determinations and calculations and as additional BP assessments for safety. For the latter, the analyses will use the Safety population.

Orthostatic hypotension evaluation

The average values of 3 recordings in supine position reported in the CRF (derived) will be used in the analysis. The recordings 1, 2 and 3 (Start after 5 minutes rest in supine position) will be only listed.

The orthostatic hypotension at each visit will be recalculated. It will be considered equal to “Yes” if at least one of the following conditions will occur:

- the average SBP after supine for 5 minutes minus the SBP 1 minute after standing is greater than 25 mmHg;
- the average SBP after supine for 5 minutes minus the SBP 3 minutes after standing is greater than 25 mmHg;
- the average DBP after supine for 5 minutes minus the DBP 1 minute after standing is greater than 15 mmHg;
- the average DBP after supine for 5 minutes minus the DBP 3 minutes after standing is greater than 15 mmHg.

Otherwise it will be considered equal to “No”.

ECG

The ECG diagnosis (normal, abnormal NCS, abnormal CS, not done, missing) will be used for the analysis.

Hematology, serum chemistry, and urinalysis

See Appendix B of the protocol for a full list of hematology, serum chemistry, and urinalysis variables that will be used for analysis. Creatinine clearance will serve dual functions as a secondary efficacy endpoint (see Section 6.2) and a safety endpoint. For the latter, the Safety population will be used for the analysis.

6.5. Other Variables

Pharmacokinetics

The plasma concentration of amlodipine at Day 14, 24 ± hour post-dose will be used for analysis.

For the individual patient data listing of amlodipine plasma concentrations, all values below the LLOQ will be reported as BLQ, as in the bioanalytical report.

For the summary of non-transformed amlodipine plasma concentration values by treatment group by descriptive statistics (n, mean, SD, median, and range), as well as the t-test analysis of the non-transformed values and the box plot analysis of non-transformed values, all BLQ values will be treated as zero.

For the summary of log-transformed amlodipine plasma concentration values by treatment group by descriptive statistics (n, mean, SD, median, and range), as well as the t-test analysis of the log-transformed values, all BLQ values will be treated as 0.04 ng/mL rather than 0. Zero cannot be log-transformed. Assignment of the BLQ values to a nonzero number will allow computation of the log transformation. The selection of 0.04 ng/mL as the nonzero number for BLQ assignment was based on the LLOQ of the validated bioanalytical method (i.e., 0.05 ng/mL) and selecting the next lowest number at the hundredth decimal place.

Baseline

Baseline measurements for the various parameters are defined as follows:

- a. ABPM baseline measurements are taken for 25 hours between Day -1 and Day 0, initiating at the Final Screening Visit and completing at Day 0 (prior to study drug administration).
- b. Baseline values for the following variables are taken on Day 0 prior to study drug administration:
 - Body weight*
 - Orthostatic hypotension evaluation
 - Vital signs (clinic visit BP measurements, pulse rate, respiration rate, and oral body temperature)*
 - Serum chemistry*
 - Targeted physical examination
- c. Baseline values for the following variable are taken at the Initial Screening Visit (Day -14 to -10) will be the baseline for the following variables:
 - BMI
 - Hematology
 - ECG
 - Urinalysis
 - Comprehensive physical examination

*Baseline measurement for body weight, vital signs, and serum chemistry is Day 0 (prior to study drug administration); however, if the baseline measurement is missing and there is a prior measurement recorded (i.e., Initial Screening Visit), this value will be carried forward and used as the baseline measurement.

7. Statistical Methodology

7.1. Handling of Missing Data

For ITT and mITT population, if at the time of the Day 7 clinic visit subjects have a too elevated BP to be able to continue safely in the study (i.e., $SBP_{24h} > 169$ mmHg or $DBP_{24h} > 110$ mmHg), blood will be drawn for renal profile testing, the study drug will be discontinued and the subjects will be instructed to resume taking their prescribed BP medication as directed by the study doctor or general practitioner. In case of missing data, LOCF techniques will be used as follows:

1. ITT population: LOCF from baseline (Day 0)
2. mITT population: LOCF from Day 6

Using this method, the end of study measurement is either Baseline, Day 6 or Day 13.

No specific analysis for withdrawn patients will be presented.

The number of patients with missing data will be presented under the “Missing” category, if present. Missing values will be included in the denominator count when computing percentages.

When continuous data are being summarized, only the non-missing values will be evaluated for computing summary statistics.

Missing or incomplete data will be treated as described in sections 5, 6.4, 6.5, 7.1, 7.9, 7.10. Other critical missing data will be discussed prior to treatment unblinding, if any. Decisions will be taken during the data review and will be fully documented in the Data Review Report.

The LOCF method of imputation will be applied for missing values in all ANCOVA models. This method will not be applied to the descriptive statistics.

7.2. Covariates and Subgroups

All ANCOVA models will include the baseline value of the variable as a covariate and treatment group as fixed effect with no interaction term.

7.3. General Methodology

Descriptive statistics will be provided for all variables in the summary tables by treatment group and overall (except where noted as treatment group only) according to the type of variable summarized.

Quantitative variables will be summarized by using n (sample size), arithmetic mean, SD, median and range (minimum and maximum).

Categorical variables will be summarized by using frequency distributions and percentages.

For the safety analyses, hypothesis testing will be carried out at the alpha = 0.05 level (two-sided) when comparing treatments. P-value will be rounded to three decimal places. Statistical significance will be declared if the rounded p-value will be less than or equal to 0.05.

All data collected in the CRF will be presented in the listings.

7.4. Patients Disposition

Disposition of patients will be presented by treatment group and overall for all patients (i.e., the Overall Trial population will be used). The summary will include the number of patients at the Initial Screening Visit, Final Screening Visit, and Day 0 visit (including patients that were not randomized), the number of patients randomized, and the number of patients at each of the remaining visits (Days 6, 7, 13, 14 and 28).

The number of patients included in each of the randomized, safety, ITT, mITT, PP and PK populations will be summarized for each treatment and overall.

The number of patients who completed the study, the number of patients who completed study treatment, and the number of patients who discontinued from the study prematurely after randomization will also be presented by treatment group and overall for the randomized population. This summary will also include a breakdown of the primary reason for discontinuation following the categories on the CRF (i.e., TEAE, withdrawal of consent, lost to follow-up, protocol deviation, study terminated, and other).

Major and minor protocol violations will be presented in the listings only.

7.5. Demographic and Screening/Baseline Characteristics

The demographic and screening/baseline characteristics will be summarized by treatment group and overall by means of descriptive statistics.

The following characteristics will be provided for the Safety population:

- Age (years)
- Sex (male/female)
- Race (white, black, Hispanic, native American, Asian, other)
- Weight (kg) at Initial Screening Visit and Day 0 (prior to study drug administration)
- Height (cm) at Initial Screening Visit
- BMI (kg/m²) at Initial Screening Visit
- Pulse rate (beats/min) at Initial Screening Visit
- Respiration rate (breaths/min) at Initial Screening Visit

- Oral body temperature (degrees Celsius) at Initial Screening Visit
- Resting SBP and DBP determined as part of manual vital signs at Initial Screening Visit (average of 3 recordings for left and right arm) and at Day 0 (average of 3 recordings for the arm with the higher average resting SBP determined as part of the manual vital signs at the Initial Screening Visit)
- ECG result at Initial Screening Visit (normal, abnormal NCS, abnormal CS, no result)
- SBP_{day}, SBP_{night}, SBP_{24h}, DBP_{day}, DBP_{night} and DBP_{24h} at baseline (Day -1 to Day 0)

Past disease and concomitant disease

Past and concomitant diseases will be coded using MedDRA dictionary (version 19.1) and frequency distributions and percentages will be summarized by treatment group for the safety population by SOC and PT.

Counts will be given for both SOC and PT by subject. Subjects experiencing more than one past disease (or concomitant disease) event within a given SOC category will be counted only once within that SOC. Similarly, subjects experiencing more than one past disease (or concomitant disease) event fitting a given PT will be counted only once for that PT.

Previous, concomitant, posterior, and unclassified medications

Medications will be coded using WHO-DD, September, 2016, using the following ATC codes:

- Anatomical Main Group (ATC 1st level code);
- Chemical subgroup (ATC 4th level code);
- Preferred name.

Previous, concomitant, posterior, and unclassified medications (as defined in Section 1.3.16) will be summarized separately for the Safety population by anatomical main group, chemical subgroup and preferred name by treatment group.

Subjects experiencing more than one previous (or concomitant or posterior or unclassified) medication within the same anatomical main group or chemical subgroup will be counted only once for that group. Similarly, subjects experiencing more than one previous (or concomitant or posterior or unclassified) medication with the same preferred name will be counted only once for that preferred name.

No formal (hypothesis testing) comparisons between treatments on baseline characteristics will be done.

7.6. Treatment Compliance and Extent of Exposure

Treatment compliance and extent of exposure as defined by the 7 parameters summarized in Section 5 will be summarized using descriptive statistics by treatment group and overall for the Safety population.

7.7. Primary Efficacy Analysis

The primary efficacy analysis is to establish the non-inferiority of amlodipine tablets (10 mg) and celecoxib capsules (200 mg) given together (arm 1) with half the effect achieved with amlodipine tablets (10 mg) given alone (celecoxib placebo) (arm 2).

Statistics are based on the change in BP from the baseline ABPM measurement (Day -1 to Day 0) to the post-dose ABPM measurement (Day 13 to Day 14 or if a LOCF is required Day 6 to Day 7), as this represents the efficacy of the treatment. As indicated below, the change will be Day 13 to Day 14 minus Baseline and so a reduction will be a negative number. Sensitivity analysis will compare the results for the ITT population with those of the PP dataset and an MMRM analysis, if possible. A sensitivity analysis will also compare the results with the mITT population.

The hypothesis test being conducted is as follows:

$$H_0: \Delta SBP_{\text{day},1} - 0.5(\Delta SBP_{\text{day},2}) \geq 0 \text{ mmHg}$$

$$H_1: \Delta SBP_{\text{day},1} - 0.5(\Delta SBP_{\text{day},2}) < 0 \text{ mmHg}$$

Where $\Delta SBP_{\text{day},1}$ is the change, for subjects in arm 1, in the SBP_{day} from the baseline ABPM measurement ($SBP_{\text{day},1,\text{base}}$) to the final ABPM measurement ($SBP_{\text{day},1,14}$).

$$\Delta SBP_{\text{day},1} = SBP_{\text{day},1,14} - SBP_{\text{day},1,\text{base}}$$

$\Delta SBP_{\text{day},2}$ is the change, for subjects in arm 2, in SBP_{day} from the baseline ABPM measurement ($SBP_{\text{day},2,0}$) to the final ABPM measurement ($SBP_{\text{day},2,14}$).

$$\Delta SBP_{\text{day},2} = SBP_{\text{day},2,14} - SBP_{\text{day},2,\text{base}}$$

This makes the actual test statistic:

$$\delta = \Delta SBP_{\text{day},1} - 0.5(\Delta SBP_{\text{day},2})$$

A one-sided 97.5% CI for δ will be computed. In addition, a two-sided non-inferiority t-test comparing δ to 0 will provide an appropriate p-value. This p-value will be computing the probability of observing a value ≥ 0 from a normal distribution for δ .

Refer to the protocol Appendix H for further details regarding the efficacy analysis, and in particular the non-inferiority margin.

7.8. Secondary Efficacy Analysis

Per the protocol, a serial gatekeeping strategy was to be used to evaluate the effect of amlodipine tablets (10 mg) and celecoxib capsules (200 mg) given together on the secondary efficacy endpoints. If and only if the statistical significance was achieved for the primary efficacy endpoint, the secondary hierarchical analysis was to be used to evaluate the secondary endpoints (i.e., body weight, SBP_{24h} , DBP_{24h} , and creatine clearance) and was only to proceed to the next endpoint in the list if the alpha is met for the prior analyses. While defining success at the secondary efficacy level will remain based on the hierarchical approach, regardless of the outcome, all four secondary efficacy endpoints (body weight, SBP_{24h} , DBP_{24h} , and creatine clearance) will be analyzed for informational purposes and to allow comparisons to the trends and statistically significant differences observed in the prior trial (KIT-302-03-01).

For all secondary efficacy endpoints, the mean change has been computed considering the difference between the value at endpoint (Day 13 to Day 14 for ABPM endpoints and Day 14 for body weight and creatinine clearance) and the value at baseline (Day -1 to Day 0 for ABPM endpoints and Day 0 pre-dose for body weight and creatinine clearance) [Endpoint – Baseline].

1. Analysis of Variance (ANOVA) will be used to compare the changes in body weight among the three treatment arms. The omni-bus test will conclude if any differences exist with post-hoc comparisons identifying specific differences between treatment arms. Any statistically significant differences will be sufficient to pass this gate in the study-wide gate keeping strategy.

$$H_0: \Delta BW_1 = \Delta BW_2 = \Delta BW_3$$

$$H_1: \text{At least one difference, } \Delta BW_i - \Delta BW_j \neq 0$$

Where ΔBW_1 is the change, for subjects in arm 1, in body weight from the baseline measurement to the post-treatment measurement.

ΔBW_2 is the change, for subjects in arm 2, in body weight from the baseline measurement to the post-treatment measurement.

ΔBW_3 is the change, for subjects in arm 3, in body weight from the baseline measurement to the post-treatment measurement.

2. A two-sample t-test for superiority will be used to test the one-sided hypothesis that treatment with amlodipine tablets (10 mg) and celecoxib capsules (200 mg) given together (arm 1) lowers SBP_{24h} to a greater degree than amlodipine tablets (10 mg) given alone (with matched celecoxib placebo) (arm 2).

$$H_0: \Delta SBP_{24h,1} - \Delta SBP_{24h,2} = 0$$

$$H_1: \Delta SBP_{24h,1} - \Delta SBP_{24h,2} > 0$$

Where $\Delta SBP_{24h,1}$ is the change, for subjects in arm 1, in SBP_{24h} from the baseline ABPM measurement to the post-treatment ABPM measurement.

$\Delta SBP_{24h,2}$ is the change, for subjects in arm 2, in SBP_{24h} from the baseline ABPM measurement to the post-treatment ABPM measurement.

3. A two-sample t-test for superiority will be used to test the one-sided hypothesis that treatment with amlodipine tablets (10 mg) and celecoxib capsules (200 mg) given together (arm 1) lowers DBP_{24h} to a greater degree than amlodipine tablets (10 mg) given alone (with matched celecoxib placebo) (arm 2).

$$H_0: \Delta DBP_{24h,1} - \Delta DBP_{24h,2} = 0$$

$$H_1: \Delta DBP_{24h,1} - \Delta DBP_{24h,2} > 0$$

Where $\Delta DBP_{24h,1}$ is the change, for subjects in arm 1, in DBP_{24h} from the baseline ABPM measurement to the post-treatment ABPM measurement.

$\Delta DBP_{24h,2}$ is the change, for subjects in arm 2, in DBP_{24h} from the baseline ABPM measurement to the post-treatment ABPM measurement.

4. A two-sample t-test for superiority will be used to test the one-sided hypothesis that treatment with amlodipine tablets (10 mg) and celecoxib capsules (200 mg) given together (arm 1) improves creatinine clearance to a greater degree than amlodipine tablets (10 mg) given alone (with matched celecoxib placebo) (arm 2).

Note: an improvement in creatine clearance is assumed to be an increase in creatinine clearance; therefore, a positive difference is an indication of improvement as shown in the following hypotheses.

$$H_0: \Delta CC_1 - \Delta CC_2 = 0$$

$$H_1: \Delta CC_1 - \Delta CC_2 > 0$$

Where ΔCC_1 is the change, for subjects in arm 1, in creatinine clearance from the baseline creatinine clearance to the post-treatment creatinine clearance.

ΔCC_2 is the change, for subjects in arm 2, in creatinine clearance from the baseline creatinine clearance to the post-treatment creatinine clearance.

7.9. Safety Analysis

AEs

PTAEs and TEAEs will be presented separately.

All AE analyses will use the Safety population. The AE listings will use the Randomized population.

See section 6.4 for AE definitions. Refer to Section 1.3.9, bullet d for further detail regarding how the PI assignments of expectedness differed from the protocol-specified definition and how this will be handled.

A summary of TEAE categories [all TEAEs, treatment emergent SAEs, ADRs, oedema events, other PTs of interest, treatment emergent UAEs, TEAEs leading to discontinuation, and TEAEs leading to death] by number of events within the category and the number and percentage of patients experiencing an event in that category will be tabulated by treatment group. Differences between groups will be evaluated using Chi-square test or Fisher's exact test (if more than 20% of the cells in a contingency table have expected counts less than 5).

AEs will be coded using the MedDRA dictionary (version 19.1). The incidence of all TEAEs will be tabulated by SOC, PT, severity and patient identification. The number of events and the number and percentage of patients with at least one event will be presented. Subjects experiencing more than one TEAE within a given SOC category will be counted only once for that SOC. Similarly, subjects experiencing more than one TEAE fitting a given PT will be counted only once for that PT. If a PT is reported more than once for a given subject, the greatest severity will be presented in the summary table.

The severity of AEs were graded as 1, 2, 3, or 4 according to WHO Toxicity Criteria (see Appendix C of protocol), or if the AEs were not included in this toxicity grading scale, they were categorized as mild, moderate, or severe per the definitions in Section 8.1.2 of the protocol. To allow for tabular summaries of severity, AEs assigned as grade 1 or mild will be included under mild, AEs assigned as grade 2 or moderate will be included under moderate, and AEs assigned as grade 3 or 4 or severe will be included under severe. Mild, moderate, and severe row headers will be presented under each PT, except in the case where there were no AEs across all treatment groups fitting a severity classification for that PT, in which case that severity classification will not be included as a row under that PT.

Similar tabular summaries will be produced for each of the following: treatment emergent SAEs, ADRs, oedema events, other PTs of interest, treatment emergent UAEs, TEAEs leading to discontinuation, PTAEs, PTAEs leading to discontinuation, and pre-treatment SAEs. In the case of the latter two, the summaries will not be produced if there are no PTAEs leading to discontinuation or pre-treatment SAEs, respectively. For the ADR summary, if an ADR is reported more than once for a given subject, the worst-case attribution will be presented in the summary table.

A comparison of TEAE rates between the amlodipine + celecoxib and amlodipine + placebo arms will be performed using an exact logistic regression model with the TEAE ("1"=At least one TEAE occurred for the patient; "0"=otherwise) as dependent variable and treatment (amlodipine + celecoxib and amlodipine + placebo) as fixed effects. The probability modeled will be TEAE="1". The number of patients and the number of patients considered in the model will be provided. The exact odds ratio of the fixed effects will be calculated (amlodipine + celecoxib and amlodipine + placebo) with the relative 95% CI and p-value.

The same model will be repeated by considering treatment-emergent SAE (“1”=At least one treatment-emergent SAE occurred for the patient; “0”=otherwise) as dependent variable, with the caveat that if no treatment-emergent SAEs are reported the table will not be produced.

The rates of oedema events between the amlodipine + celecoxib arm and the amlodipine + placebo arm will be compared using an exact logistic regression and reporting the odds ratio. Oedema event (1 = at least one TEAE with PT of oedema, oedema peripheral, peripheral swelling, swelling, or joint swelling occurring for the subject; 0 = otherwise) will be the dependent variable, and treatment (amlodipine + celecoxib and amlodipine + placebo) will be the fixed effects.

The Fisher’s exact test will be run to compare the number of oedema events that occurred while on treatment (Day 0 to Day 14+1) and post-treatment (>Day 14+1) between treatment arms 1 and 2 (amlodipine + celecoxib and amlodipine + placebo).

Comprehensive physical examination

Each protocol-specified organ or body system for the comprehensive physical examination will be summarized for the Safety population by a shift table presenting the number and the percentage of patients in each bivariate category (Initial Screening Visit versus Day 14) with regards to Investigator’s interpretation (normal, abnormal NCS, abnormal CS, not done, and missing) by treatment group.

The results of targeted physical examination will be only listed.

Body weight

Body weight will be summarized for the Safety population by treatment group at each applicable visit (Initial Screening Visit, Day 0, Day 7 and Day 14) by descriptive statistics (n, mean, SD, median, and range). In addition, at each visit after baseline, change from baseline will be calculated and summarized by descriptive statistics (n, mean, SD, median, and range). Baseline will be Day 0 if available, otherwise, the Initial Screening Visit assessment will be used.

A comparison between treatment groups with an ANCOVA model, with change from baseline to Day 14 as dependent variable, treatment as fixed effect and baseline as covariate. A LOCF method of imputation will be applied for missing values. The number of patients and the number of patients considered in the model will be provided by treatment. P-values of the fixed effects and covariates will also be presented. The adjusted means for treatments and the relative 95% CIs will be presented. The difference between the adjusted means of the three treatment groups will be calculated with the relative 95% CI and p value.

Vital signs other than BP

Pulse rate (beats/min), respiration rate (breaths/min), and oral body temperature (degrees Celsius) will be summarized for the Safety population by treatment group at each applicable visit (Initial Screening Visit, Day 0, Day 7, Day 14, and Day 28) by descriptive statistics (n, mean, SD, median, and range). In addition, at each visit after baseline, change from baseline will be calculated and summarized by descriptive statistics (n, mean, SD, median, and range). Baseline will be Day 0 if available, otherwise, the Initial Screening Visit assessment will be used.

Vital signs - BP

Clinic visit average resting SBP and DBP (mmHg) will be summarized for the Safety population by treatment group at each applicable visit (Initial Screening Visit, Day 0, Day 7, Day 14, and Day 28) by descriptive statistics (n, mean, SD, median, and range). In addition, at each visit after baseline, change from baseline will be calculated and summarized by descriptive statistics (n, mean, SD, median, and range). Baseline will be Day 0 if available, otherwise, the Initial Screening Visit assessment will be used.

For each variable (average resting SBP and DBP) a comparison between treatment groups will be performed with an ANCOVA model with change from baseline to Day 14 as dependent variable, treatment as fixed effect and baseline as covariate. A LOCF method of imputation will be applied for missing values. In the event there is no Day 14 measurement, the Day 7 measurement will be carried forward. Baseline measurement is Day 0 (prior to study drug administration); however, in the event the Day 0 measurement is missing, the Initial Screening Visit measurement will be carried forward. The number of patients and the number of patients considered in the model will be provided by treatment. The adjusted means for treatments and the relative 95% CIs and p values will be presented. The difference between the adjusted means of the three treatment groups will be calculated with the relative 95% CI and p-value.

Continuous monitoring of BP

SBP_{day}, SBP_{night}, SBP_{24h}, DBP_{day}, DBP_{night}, and DBP_{24h} (mmHg) will be summarized for the Safety population by treatment group at each applicable visit (Day -1 to Day 0, Day 6 to Day 7, and Day 13 to Day 14) by descriptive statistics (n, mean, SD, median, and range). In addition, at each visit after baseline, change from baseline will be calculated and summarized by descriptive statistics (n, mean, SD, median, and range). Baseline will be Day -1 to Day 0.

Orthostatic hypotension evaluation

The orthostatic hypotension evaluation BP values will be summarized for the Safety population by treatment group at each applicable visit (Day 0, Day 7, and Day 14) by descriptive statistics (n, mean, SD, median, and range). In addition, at each visit after baseline, change from baseline will be calculated and summarized by descriptive statistics (n, mean, SD, median, and range). Baseline will be Day 0. The above analysis will be performed for each of the following:

1. Average BP after 5 minutes rest in supine position (average of 3 recordings)
 - a. SBP
 - b. DBP
2. BP 1 minute after standing
 - a. SBP
 - b. DBP
3. BP 3 minutes after standing
 - a. SBP
 - b. DBP
4. Difference between average BP after 5 minutes rest supine and BP 1 minute after standing
 - a. SBP
 - b. DBP
5. Difference between average BP after 5 minutes rest supine and BP 3 minutes after standing
 - a. SBP
 - b. DBP

Comparisons of the orthostatic hypotension BP measurements among treatment arms using ANCOVA will be presented for each of the above 5 parameters. The change from baseline to Day 14 will be considered.

The number and the percentage of patients with evidence of Orthostatic Hypotension (Yes, No, Missing) will be presented at each visit (Day 0, Day 7, and Day 14) by treatment group. The Chi-Squared/Fisher's Exact test will be provided to test differences between arms.

Laboratory parameters

Hematology, chemistry and urinalysis (including urine microscopy) parameters will be summarized for the Safety population by treatment group at each applicable visit (Initial Screening Visit, Day 0*,

Day 7*, and Day 14) by descriptive statistics as appropriate (i.e., n, mean, SD, median, and range for continuous data and frequency for categorical data). In addition, at each visit after baseline, change from baseline will be calculated and summarized for continuous data by descriptive statistics (n, mean, SD, median, and range). Baseline will be Day 0 if available, otherwise, the Initial Screening Visit assessment will be used.

*The laboratory parameters on Day 0 and Day 7 were limited to serum chemistry tests (i.e., no hematology or urinalysis), and further, the serum chemistry tests at Day 7 were limited to creatinine (and calculation of creatinine clearance) and electrolytes (sodium, bicarbonate, calcium, chloride, phosphorous, and potassium).

Shift tables presenting the number and the percentage of patients in each bivariate category (Baseline versus Day 14) with regards to reference range (Low, Normal, High, missing) will be provided for all laboratory parameters by treatment group. Baseline will be Day 0 if available, otherwise, the Initial Screening Visit assessment will be used.

The laboratory reference range for assigning low “L” flags to the creatinine clearance results differed for the Celerion, Belfast laboratory (>90 mL/min) versus the centralized laboratory used for the remaining sites (ACM Global Central Laboratories; ≥ 60 mL/min). The serum chemistry shift table analysis will be based on the laboratory assigned flags (i.e., no reassignment of the Celerion, Belfast laboratory flags based on the ACM laboratory reference range will be made). The main body of the clinical study report will note the difference in the creatinine clearance reference range for the two laboratories and will note by treatment group any cases where a Celerion, Belfast low creatinine clearance value would be reassigned as Normal if the ≥ 60 mL/min criterion was used.

For serum creatinine and BUN, comparisons between treatment groups will be performed with an ANCOVA model with change from baseline to Day 14 as dependent variable, treatment as fixed effect and baseline as covariate. The number of patients and the number of patients considered in the model will be provided by treatment. P-values of the fixed effects and covariates will also be presented. The adjusted means for treatments and the relative 95% CIs will be presented. The difference between the adjusted means of the three treatment groups will be calculated with the relative 95% CI and p-value.

The primary comparison will be treatment group 1 compared to treatment group 2, and the key secondary comparison will be treatment group 1 compared to treatment group 3. In these analyses, the null hypothesis will be that there is no statistically significant difference in the change in the measured blood parameter (serum creatinine or BUN) from baseline to the end of treatment between the two treatment groups. Baseline will be Day 0 if available, otherwise, the Initial Screening Visit assessment will be used.

The listings and summary tables will use the clinical laboratory test names as they appear in the Study Data Tabulation Model dataset files (i.e., the Clinical Data Interchange Standards Consortium compliant clinical laboratory test names). Refer to “Note to File - Differences in Laboratory Test Names Between Testing Laboratory and Study Data Tabulation Model (SDTM) Files”, a copy of which is available in the Trial Master File.

12-Lead ECG

The 12-Lead ECG diagnoses will be summarized for the Safety population by a shift table presenting the number and the percentage of patients in each bivariate category (Initial Screening Visit versus Day 14) with regards to Investigator’s interpretation (Normal, Abnormal NCS, Abnormal CS, Not done) will be provided by treatment group.

7.10. Additional Analyses

A set of additional analyses will be performed, which will include testing of pharmacokinetics, BP at peak and trough amlodipine concentrations, sensitivity analyses, exploratory and other efficacy analyses, and Investigational Site-specific analyses.

Pharmacokinetics

For the individual patient data listing of amlodipine plasma concentrations, all values below the LLOQ will be reported as BLQ, as in the bioanalytical report.

Non-transformed amlodipine plasma concentration values at Day 14 will be summarized for the PK population by treatment group by descriptive statistics (n, mean, SD, median, and range). A t-test will compare the non-transformed amlodipine plasma concentration values in those subjects who receive amlodipine tablets (10 mg) given alone (with matched celecoxib placebo) (arm 2) with those who receive amlodipine tablets (10 mg) and celecoxib capsules (200 mg) given together (arm 1). A box plot of the non-transformed amlodipine plasma concentrations at Day 14 by treatment arm will be produced. For these analyses, BLQ values will be treated as 0, and only treatment arms that included amlodipine will be included (i.e., the placebo + placebo arm will not be included).

Log-transformed amlodipine plasma concentration values at Day 14 will be summarized for the PK population by treatment group by descriptive statistics (n, mean, SD, median, and range). A t-test will compare the log-transformed amlodipine plasma concentration values in those subjects who receive amlodipine tablets (10 mg) given alone (with matched celecoxib placebo) (arm 2) with those who receive amlodipine tablets (10 mg) and celecoxib capsules (200 mg) given together (arm 1). For these analyses, only treatment arms that included amlodipine will be included (i.e., the placebo + placebo arm will not be included). Further, all BLQ values will be treated as 0.04 ng/mL rather than 0. Zero cannot be log-transformed. Assignment of the BLQ values to a nonzero number will allow computation of the log transformation. The selection of 0.04 ng/mL as the nonzero number for BLQ assignment was based on the LLOQ of the validated bioanalytical method (i.e., 0.05 ng/mL) and selecting the next lowest number at the hundredth decimal place.

Peak and trough

SBP and DBP at the expected peak and trough amlodipine concentrations will be summarized for the ITT population by treatment group at Day 6 and Day 13 by descriptive statistics (n, mean, SD, median, and range). Additionally, the difference between Day 6 and Day 13 will be calculated and summarized by descriptive statistics (n, mean, SD, median, and range).

For each variable (SBP peak, SBP trough, DBP peak, and DBP trough) a comparison between treatment groups will be performed with a two-sample t-test of the change from Day 6 to Day 13. A LOCF method of imputation will not be applied for missing values. The p-value will be evaluated on a two-sided t-test.

The trough BP (SBP and DBP) is the ambulatory BP measurement taken closest to the time of study drug administration on Study Day 6 or Day 13, respectively, that is also before the time of study drug administration that day. If there is no ambulatory measurement prior to administration of study drug on Study Day 6 or Day 13, the first ambulatory measurement after study drug administration that day will be used as trough.

The peak BP (SBP and DBP) is the ambulatory BP measurement taken closest to the time point 9 hours after study drug is administered on Study Day 6 or Day 13, respectively, that is also before the time point 9 hours after the study drug is administered that day. Based on the approved labeling for amlodipine besylate tablets, the expected peak time for amlodipine is 6 to 12 hours after the medication is administered, and thus the midway point (9 hours) was selected for this analysis.

Sensitivity analyses

A sensitivity analysis will be conducted to insure the change in definition of the ITT population (see Section 1.3.2) does not impact the study conclusions. A mITT population will be based on the definition originally presented as the ITT population in the protocol (valid Baseline and at least one valid follow-up ABPM measurement) and a second set of analyses will be conducted purely to demonstrate the definition does not have an impact on the primary and secondary efficacy analyses. The following analyses will be conducted:

1. mITT for SBP_{day}
2. mITT for SBP_{24h}
3. mITT for DBP_{24h}

The impact of defining valid ABPM measurements based on valid daytime measurements for the efficacy analyses (see Section 1.3.1 for further detail) is that the analyses of the secondary ABPM efficacy parameters (SBP_{24h} and DBP_{24h}) and exploratory ABPM efficacy parameters (SBP_{night} and DBP_{night}) may include invalid measurements with respect to the 24-hour period (i.e., may not meet criterion d or e in Section 1.3.1) or night-time period (i.e., may not meet criterion d in Section 1.3.1), respectively. It is anticipated that this will be a very small number of cases and will not impact the secondary and exploratory ABPM efficacy conclusions drawn. Sensitivity analyses will be conducted to verify this point. The following analyses will be conducted:

1. ITT for SBP_{24h} excluding SBP_{24h} values that had an entry of valid for day validity and an entry of invalid for night or 24h validity (i.e., did not meet criterion d or e, respectively)
2. ITT for DBP_{24h} excluding DBP_{24h} values that had an entry of valid for day validity and an entry of invalid for night or 24h validity (i.e., did not meet criterion d or e, respectively)
3. ITT for SBP_{night} excluding SBP_{night} values that had an entry of valid for day validity and an entry of invalid for night validity (i.e., did not meet criterion d)
4. ITT for DBP_{night} excluding DBP_{night} values that had an entry of valid for day validity and an entry of invalid for night validity (i.e., did not meet criterion d)

To assess the impact of baseline, a further sensitivity analysis will be conducted on the primary endpoint (mean change of SBP_{day}) using a regression model adjusted from Baseline on ITT, mITT, and PP populations.

Exploratory efficacy analyses

Exploratory efficacy analyses will include two-sample t-tests to test one-side hypotheses of superiority for pairwise comparisons between treatment arms 1 and 2, 1 and 3, and 2 and 3 for DBP_{day}, SBP_{night} and DBP_{night}.

Further, two-sample t-tests to test one-side hypotheses of superiority for pairwise comparisons between treatment arms 1 and 3 and 2 and 3 will be performed for SBP_{day}, SBP_{24h}, and DBP_{24h} (the comparison of treatment arms 1 and 2 for these endpoints are covered separately under the respective primary and secondary efficacy analyses).

All exploratory efficacy comparisons will be based on the mean reduction in BP from the baseline (Day -1 to Day 0) ABPM measurement to the Day 13 to Day 14 ABPM measurement (or if a LOCF was required, the Day 6 to Day 7 ABPM measurement). The analyses will use the ITT data set including LOCF (and MMRM if possible) for subjects who were withdrawn from treatment early. Sensitivity analyses will be used to compare these results to those of the PP data set.

Investigational Site-specific analyses

An Investigational Site-specific summary tabulation for the Safety Population, including demographic characteristics (age, sex and race), Initial Screening Visit characteristics (height, weight, BMI, pulse

rate, respiration rate, oral body temperature, SBP left arm, SBP right arm, DPB left arm, DBP right arm, and ECG), and Baseline Day 0 characteristics (weight, SBP, and DBP) by treatment arm and overall will be presented. The Day 0 SBP and DBP to be included in this table will be for the arm with the higher average resting SBP determined as part of the manual vital signs at the Initial Screening Visit. Descriptive statistics will be generated as appropriate (i.e., n, mean, SD, median and range for continuous data and number and percentage of patients for categorical data).

An Investigational Site-specific summary tabulation for the Safety Population, including SBP_{day}, SBP_{night}, SBP_{24h}, DBP_{day}, DBP_{night} and DBP_{24h} at baseline (Day -1 to Day 0) by treatment arm and overall will be presented. The table will include pooled values (i.e., for all sites) as well. Descriptive statistics will be generated (i.e., n, mean, SD, median and range).

A summary tabulation for the ITT population, including the mean \pm SD SBP_{day} at baseline, end of study, and the change from baseline to end of study for the patients at Sites 301 (Queen Mary School of Medicine & Dentistry), 302 (Celerion, Belfast), 303 (Rowden Surgery), and 304 (Medicines Evaluation Unit), the four largest recruiting sites, and the patients at all remaining sites (pooled) by treatment arm will be presented as a means of evaluating the comparability of the primary efficacy endpoint across sites. Pooling of data for 4 of the 8 sites (that randomized patients) will be done due to the small numbers of patients per treatment arm per Investigational Site. The table will also include a row that includes the summary statistics for the whole ITT population (i.e., including all sites) for comparison.

8. General Considerations

8.1. Software to be used

All statistical analyses and data processing will be performed using SAS version 9.4 or higher.

8.2. Programs and Tables Quality Control

The following procedures will be implemented as quality control measures:

- Double-blind programming, ensuring that the code gives the required output and the programming is in compliance with any applicable specifications from the analysis plan
- Check for errors and warning messages
- Check of the layout of the listings and tables

Additionally, in the course of data collection eCRF data will be reviewed and queries raised if needed.

9. Data Storage

Relevant study documentation will be stored in the “*Buncro*” – private StatisticaMedica cloud hosted by *Radix Technologies*, in *Kitov 302-03-02/Programming* for the scripts and *Kitov 302-03-02/Reports* for the delivered documentation, in the corresponding subfolders for the SAP, TFLs and CSR.

Appendices

Appendix A. ABPM Measurement Specifics

ABPM Measurement Weighting

Each measurement shall be weighted according to half the duration to the preceding measurement and half the duration to the succeeding measurement up to maxima of half the expected intervals as follows:

| <u>Time of Day (in minutes)</u> | <u>Max Preceding Weight</u> | <u>Max Succeeding Weight</u> |
|--|-----------------------------|------------------------------|
| 09:00 to 09:20 (540 to 560) | 15 min | 10 min |
| 09:21 to 21:39 (550 to 1299) | 10 min | 10 min |
| 21:40 to 21:59 (1300 to 1319) | 10 min | 15 min |
| 22:00 to 08:59 (0 to 539 and 1320 to 1439) | 15 min | 15 min |

All statistics shall be based on weighted measurements. For daytime and night-time statistics, weights for the first measurements within the respective periods shall be truncated at the start of the period and weights for the last measurements within the respective periods shall be truncated at the end of the period.

Hourly mean pressures shall be based on the weights of measurements occurring within the hour. Each hour shall be defined by " $m \setminus 60$ ", where m is the number of minutes from midnight on the day the monitor is fitted and \setminus represents the quotient of the Euclidian division. ($m \equiv (m \setminus 60) \times 60 + m \bmod 60$)

ABPM Study Measurements

A measurement shall be regarded as valid if it contains values for systolic blood pressure (SBP), diastolic blood pressure (DBP) and heart rate (HR) and

SBP is between 50 mmHg and 300 mmHg.

DBP is between 40 mmHg and 150 mmHg.

Pulse pressure is between 10 mmHg and 150 mmHg.

HR is between 40 bpm and 150 bpm.

The first study measurement shall be

The nearest valid measurement to the drug intake time on the day the monitor is fitted that is both a) between 07:00 and 10:00 and b) within 15 minutes of the drug intake time.

If there is no valid measurement within this period, a 1-hour grace period is permitted. It is, therefore, the nearest valid measurement to the drug intake time on the day the monitor is fitted that is both a) between 06:00 and 11:00 and b) within 75 minutes of the drug intake time.

If there is no valid measurement within this period, or if no drug intake time is recorded (e.g., Day-1), the first valid measurement recorded between 07:00 and 10:00.

If there is no valid measurement within this period, the first valid measurement recorded between 06:00 and 11:00.

If there is no valid measurement within this period, the nearest valid measurement to the drug intake time on the day the monitor is fitted, if that is recorded, or first valid measurement otherwise.

Measurements recorded during the first hour, from the first study measurement, shall be regarded as white-coat window measurements. The period covered by these measurements defines the white-coat window.

The last study measurements shall be

The earliest valid measurement that is a) at least 25 h after the first study measurement b) at least 25 h after the drug intake time on the day the monitor is fitted and c) less than 25 h after the end of the white-coat window

If there is no valid measurement within this period, a 1-hour grace period is permitted. It is, therefore, the earliest valid measurement that is a) at least 24 h after the first study measurement b) at least 24 h after the drug intake time on the day the monitor is fitted and c) less than 26 h after the end of the white-coat window

If there is no valid measurement within this period, the latest measurement that is less than 26 h after the end of the white-coat window.

Measurements before the first study measurement and measurements after the last study measurement shall be disregarded.

Invalid measurements and measurements that result in an error shall not be regarded as study measurements.

Measurements recorded during the white-coat window are not included in daytime, night-time and 24 h statistics.

ABPM Validity

An ABPM measurement shall be defined as valid overall if the data comply with the following criteria:

The time of the first study measurement is between 07:00 and 10:00.

The duration, from the first study measurement to the last study measurement, is at least 25 h (1500 min).

There are at least 21 study measurements recorded during the standard daytime period (09:00 to 21:00)

There are at least 8 study measurements recorded during the standard night-time period (01:00 to 06:00)

There are at least 35 study measurements recorded after the white-coat window

There are no more than 3 hours with a total measurement weight of less than 20 min and no more than 2 consecutive hours with total measurement weights each of less than 20 min.

For the purpose of defining the ITT, mITT, and PP populations, a visit measurement will be valid if the Daytime measurement is valid.

An ABPM measurement shall be defined as valid within tolerance if the data comply with the following criteria:

The time, of the first study measurement is between 06:00 and 11:00.

The duration, from the first study measurement to the last study measurement, is at least 24 h (1440 min).

There are at least 20 study measurements recorded during the standard daytime period (09:00 to 21:00)

There are at least 7 study measurements recorded during the standard night-time period (01:00 to 06:00)

There are at least 34 study measurements recorded after the white-coat window

There are no more than 3 hours with a total measurement weight of less than 20 min and no more than 2 consecutive hours with total measurement weights each of less than 20 min.

An ABPM measurement shall be defined as invalid if it is not valid within tolerance.

ABPM Statistics

Average 24-hour, daytime and night-time pressures are calculated as

$$\bar{v}_{p,r} = \frac{\sum_{i=FSM}^{LSM} v_{r,i} w_{p,i}}{\sum_{i=FSM}^{LSM} w_{p,i}}$$

where r is SBP or DBP

p is 24-hour, daytime or night-time

$v_{r,i}$ is the SBP or DBP for measurement i

$w_{p,i}$ is the weight of the measurement for period p , zero if the measurement does not belong to that period

FSM is the first study measurement

LSM is the last study measurement

2) The SDs are calculated as

$$s_{p,r} = \sqrt{\frac{\sum_{i=FSM}^{LSM} v_{r,i}^2 w_{p,i} - \bar{v}_{p,r}^2 \sum_{i=FSM}^{LSM} w_{p,i}}{\frac{M_p - 1}{M_p} \sum_{i=FSM}^{LSM} w_{p,i}}}$$

where M_p is the number of non-zero weighted measurements in period p