CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

210045Orig1s000

STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA: Supplement:	210045
Drug Name:	celecoxib and amlodipine besylate
Indication(s):	Subjects with hypertension requiring antihypertensive therapy
Applicant:	Kitov Pharmaceuticals, Ltd.
Date(s):	July 31, 2017
Review Priority:	Standard
Biometrics Division:	DBI/OB/OTS
Statistical Reviewer:	Fanhui Kong, PhD
Concurring Reviewers:	Hsien Ming Hung, PhD
Medical Division:	Division of Cardiovascular and Renal Products
Clinical Team:	Tzu-Yun (Z) McDowell, MD
CDTL	Shari Targum, MD.
Project Manager:	Sabry Soukehal

Keywords: Day Sitting Systolic Blood Pressure (SBP_{day}), Day Sitting Diastolic Blood Pressure (DBP_{day}), Non-Inferiority Test, Last Observation Carried Forward (LOCF)

Table of Contents

1 EXECUTIVE SUMMARY

KIT-302 is an oral fixed combination drug product consisting of the non-steroidal anti-inflammatory drug (NSAID) celecoxib and the calcium channel blocker antihypertensive drug amlodipine besylate. In this NDA the sponsor seeks the regulatory approval of KIT-302 for (b) (4) osteoarthritis for the patients who require (b) (4) treatment of hypertension to lower blood pressure (BP).

The pivotal study KIT-302 was a multi-center, randomized, double blind, placebo controlled study to evaluate the effect of celecoxib on the efficacy and safety of amlodipine and to evaluate PK drug-drug interactions in subjects with hypertension requiring antihypertensive therapy. Eligible subjects were randomized 1.5:1.5:1:1 to one of the four treatment arms: amlodipine + celecoxib, amlodipine, celecoxib, and placebo. The primary objective was to demonstrate that the mean reduction of the daytime (9:00 to 21:00) ambulatory systolic blood pressure (SBP_{day}) of the amlodipine + celecoxib arm in adult subjects with newly diagnosed hypertension was no less than half of that in the amlodipine monotherapy arm. A secondary comparison was made between Arms 3 and 4 to determine if celecoxib resulted in a statistically significant increase in SBP_{day} compared to placebo.

With a total of 152 randomized patients received at least one administration of the study drugs and 150 in the ITT population, the primary efficacy analysis of the study indicated that the combination therapy retained at least half the effect of amlodipine on SBP_{day} and therefore provided the evidence supporting the indication of KIT-302 (b) (4) of osteoarthritis for the patients who require the treatment of hypertension. The secondary comparison of the same efficacy endpoint between the celecoxib and placebo arms yielded a numerical difference in favor of the placebo, but did not reach statistical significance to support the assertion that the celecoxib monotherapy gave less reduction than placebo in the systolic daytime blood pressure.

2 INTRODUCTION

KIT-302 is a fixed combination drug product (FCDP) consisting of the non-steroidal anti-inflammatory drug (NSAID) celecoxib and the calcium channel blocker antihypertensive drug amlodipine besylate. Both celecoxib and amlodipine besylate are marketed in the United States and worldwide as individual branded and generic prescription drug products (celecoxib and amlodipine besylate were first approved in 1998 and 1992, respectively). The sponsor intended to indicate KIT-302 for (b) (4) treatment (b) (4) of osteoarthritis for the patients who require (b) (4) treatment of hypertension to lower blood pressure (BP).

This NDA relied on FDA's previous findings of safety and effectiveness for the individual reference listed drugs (RLDs): NDA 020998 for Celebrex® (celecoxib) capsules and NDA 019787 for Norvasc® (amlodipine besylate) tablets. Per agreement with FDA, a single pivotal efficacy trial (Study KIT-302) was conducted in support of this NDA.

This was a multi-center, randomized, double-blind, placebo and actively controlled study to evaluate the effect of celecoxib on the efficacy and safety of amlodipine and to evaluate for pharmacokinetic (PK) drug-drug interactions (DDIs) in subjects with newly diagnosed hypertension who required pharmacological therapy to control their hypertension. The combination therapy of amlodipine + celecoxib was considered effective if it kept half of the effect on the mean reduction, or minus of the mean change, of SBP_{day} of the amlodipine monotherapy.

The primary efficacy comparison was conducted in the ITT population. In the analysis, the effectiveness of the combination therapy in keeping half the effect of amlodipine on the mean reduction of SBP_{day} was tested using a problematic statistical method that did not take into account the variability of the observed mean SBP_{day} reduction of the amlodipine. The statistical reviewer revised the method and reanalyzed the data and gave the results that supported the sponsor's conclusion.

2.1 Overview

In the pivotal study of KIT-302, eligible subjects were randomized 1.5:1.5:1:1 to one of four treatment arms: amlodipine + celecoxib, amlodipine, celecoxib, and placebo. The primary objective was to demonstrate that the mean reduction of SBP_{day} of the amlodipine + celecoxib arm was no less than half of that in the amlodipine arm in adult subjects with newly diagnosed hypertension. According to the clinical study report (CSR), a sample of 152 patients were randomized to one of the four treatment arms: 49 to the amlodipine + celecoxib arm, 45 to amlodipine arm, 31 to celecoxib arm, and 27 to placebo arm. The comparison of the change from baseline of SBP_{day} between the amlodipine + celecoxib and amlodipine arms yielded a difference of -1.77 mmHg with a 95% CI of -5.35 to 1.81 mmHg ($p = 0.329$). Since the upper bound of this CI was below -1/2 of the estimated mean change from baseline of SBP_{day} in the amlodipine arm which was 4.41 mmHg, the sponsor concluded that the combination therapy was statistically

non-inferior to the amlodipine monotherapy. As the primary efficacy comparison was statistically significant, the secondary comparison for the superiority of placebo over celecoxib was performed. This yielded a difference between the two mean changes of SBP_{day} of 1.58 mmHg with a 95% CI of -2.99 to 6.15 mmHg ($p = 0.49$), which was not statistically significant. As the consequence, the tertiary comparison between the combination and the celecoxib arms was not performed.

The statistical reviewer considered the sponsor's primary statistical comparison problematic. By comparing the upper bound of the 95% CI for the difference of the primary endpoint of the mean changes of SBP_{day} from baseline between the combination therapy and the amlodipine therapy directly with -1/2 of the estimated mean change of SBP_{day} in the amlodipine arm, the sponsor ignored the variability of the latter. As an alternative, the statistical reviewer compared the difference of the primary endpoint between the combination therapy and ½ of that in the amlodipine arm alone. Comparing the upper bound of the 95% CI of the difference with zero gives a statistically valid test. The new analysis yielded a 95% CI of -9.15 to -3.21 mmHg for the difference which was below zero ($p < 0.001$) and therefore gave the evidence supporting the conclusion of the sponsor.

2.2 Data Sources

The sponsor's electronic data sources were stored in the directory of \\CDSESUB1\evsprod\NDA210045\0001 of the electronic document room of the Agency. Data sources include all material reviewed, i.e., study reports, raw data sets in SDTM format, analysis data sets in ADAM format, SAS programs for deriving the data sets and analysis results, protocol amendments, individual data listings, reporting and statistical analysis plan, and literature referenced, etc. The SAS data sets are stored in the directory of \\CDSESUB1\evsprod\NDA210045\0001\m5\datasets\. The analysis software is also stored in the same directory.

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

The sponsor provided high quality data sets along with the programs to produce the analysis data sets and efficacy results which allowed the statistical reviewer to duplicate the efficacy results. According to the CSR, a computer-generated randomization schedule was used to assign subjects to treatment arms. Randomization codes, all treatments dispensed to the patients and all dosage changes were tracked. A central laboratory was used for the ambulatory blood pressure monitor (ABPM) reading to standardize the results across all investigational sites. The contract research organization (CRO) staff responsible for reading the ABPM data was blinded to treatment arm assignment. After categorization of the major and minor protocol deviations was finalized and the database was declared to be complete and accurate, it was locked and the treatment codes were unblinded and released for statistical analyses and the database was frozen. The freeze form was completed by the data manager (DM) to document the activity. With database freeze, all accesses to the eCRF was restricted to browse only for external users, while access for internal DMs was disabled with the exception of the Lead DM.

The CSR also indicates that all the clinical sites were carefully monitored before initiating the study and during the study to assure that all necessary equipment and supplies (e.g., ABPMs and patient diary cards) were on hand, the standard operating procedures (SOPs) and the Good Clinical Practice (GCP) were fully adhered, and that the data entered into the eCRFs were complete and accurate. The investigators were required to maintain source documents for each patient in the study. All information on eCRFs was required to be traceable to these source documents in the patient's file. The quality assurance of the internal system (internal processes, clinical development functions/units, etc.), investigator site, and third party/vendors were audited by an outside auditor.

3.2 Evaluation of Efficacy

3.2.1 Study Design and Endpoints

Following an up to 7-day screening phase, eligible subjects were randomized to one of the 4 treatment arms. All drugs were administered orally once a day, over-encapsulated (OE) for a total of 14 doses. Visits at the clinic took place at study Day 0 (start of treatment), Days 1, 6, 7, 13 (end of treatment), 14 and 28 (end of follow-up). Approximately 150 adult subjects with newly diagnosed hypertension requiring pharmacological therapy to control their hypertension were randomized 1.5:1.5:1:1 to one of the following four treatment arms.

Arm 1: OE 10 mg amlodipine tablet + OE 200 mg celecoxib capsule (named amlodipine + celecoxib arm);
Arm 2: OE 10 mg amlodipine tablet + matched placebo for celecoxib (named amlodipine arm);
Arm 3: Matched placebo for amlodipine + OE 200 mg celecoxib capsule (named celecoxib arm);
Arm 4: Matched placebo for both amlodipine and celecoxib (named placebo arm).

Per the final version of the protocol (Version 14), an adaptive design was used to determine the sample size requirement for this trial. After the initial 150 subjects had been randomized, additional subjects were to be enrolled and randomized into either treatment Arm 1 or 2 at a 1:1 ratio until the interim analysis had been completed and a decision had been made whether or not additional subjects were required. The subjects randomized during this period were to be included in all analyses regardless of whether additional subjects were required. If the interim analysis indicated that more subjects were required, the new subjects were to be randomized into Arms 1 and 2 in a 1:1 ratio until the required number of subjects were met. If the interim analysis indicated that no further subjects were required, the study was to be halted.

The sample size was based on testing the hypothesis that the reduction in mean SBP_{day} in the combination arm was at least half of that in the amlodipine arm. Since the observed standard deviation was not able to obtain, the sponsor started with 150 subjects in the adaptive design and conducted an interim analysis by an independent statistician to estimate the standard deviation to finalize the sample size. The interim analysis indicated that no additional sample was needed. The use of a placebo arm in the study minimized the risk of biases in the evaluation of the effects of amlodipine and celecoxib given in combination or as single agents. Such a study design was requested by FDA at a pre-IND meeting for another of Kitov's fixed combination drug products (FCDPs) and it was later proved by the Agency.

According to CSR, the study protocol of KIT-302 was amended 13 times, and there were a total of 14 versions. The first patient visit occurred under Version 7. The protocol submissions to FDA started with Version 1. Protocol changes after Version 7 were recorded in Appendix 16.1.1 of the CSR. In Version 10, the primary efficacy endpoint was changed from the mean 24-hour ambulatory systolic blood pressure (SBP_{24h}) to the mean daytime ambulatory systolic blood pressure (SBP_{day}). The same change was also made to the secondary and tertiary efficacy endpoints. In the meantime, it was clarified that a drop of 9 mmHg in SBP_{day} was a reasonable

and consistent estimate for M1 (the whole effect of the active control of amlodipine) for the non-inferiority test throughout the ABPM assessments. In Version 11, it was clarified that in the interim analysis a margin M2 of 4.5 mmHg would be used to find the pooled standard deviation for the difference between the mean SBP_{day} values. It was further revised that this pooled standard deviation was used for the determination of the sample size.

Primary and Secondary Endpoints:

The primary efficacy endpoint for this trial was the mean change in SBP_{day} from baseline (Day –1 to Day 0) to the study end (Day 13 to Day 14), or to Day 6 to Day 7, or to Day 0 to Day 1 where a subject withdrew from the treatment program. The primary efficacy analysis was the comparison between Arm 1 and Arm 2. The combination therapy was declared to be non-inferiority to the amlodipine monotherapy if it kept no less than half the mean reduction in SBP_{day} of the amlodipine monotherapy. Secondary endpoints included the differences, between Arms 1 and 4, in the mean change in SBP_{day} between Arms 1 and 2, 3 and 4, in the mean changes in SBP_{24h}, SBP_{night}, DBP_{24h}, DBP_{day} and DBP_{night}, as measured by ABPM, from Day 0 to Day 14.

This study was conducted at 11 sites in the United Kingdom (UK). The number of subjects enrolled at each site ranged from 0 to 12 for the amlodipine + celecoxib arm, 0 to 11 for the amlodipine arm, 0 to 7 for the celecoxib arm, and 0 to 7 for the placebo arm. The first visit for the first patient was taken on June 26, 2014 and the last visit for the last patient was taken on November 19, 2015.

3.2.2 Statistical Methodologies

The statistical analysis plan (SAP) was finalized on April 14, 2017 before data unblinding. The ITT data set was used for the primary comparison, with LOCF for the subjects who withdrew before the end of the study.

The ITT population consisted of all randomized subjects with at least a valid Baseline (Day –1 to Day 0) ABPM measurement and either

- A valid final (Day 13 to Day 14) ABPM measurement, where a subject completed the treatment program; or
- A valid Day 6 to Day 7 ABPM measurement, or Day 0 to Day 1 ABPM measurement, if the subject withdrew from the treatment program at that point because of an $SBP_{24h} >$ 169 mmHg and/or a $DBP_{24h} > 110$ mmHg, or for any other reason.

As indicated in the final SAP, a two-sample *t*-test was used to determine if the amlodipine + celecoxib combination therapy was non-inferior to the amlodipine monotherapy. The non-inferiority would be concluded if the lower limit of the 95% CI for the difference in SBP_{day} reduction between the combination and the amlodipine was above 1/2 of the estimated mean reduction of the latter, in other words, if the upper limit of the 95% CI for the difference in

SBP_{day} change between the combination and the amlodipine therapy was below -1/2 of the mean change in the latter.

A serial testing procedure was designed for the primary, secondary and tertiary comparisons. If the primary efficacy test was statistically significant, the secondary efficacy comparison (between Arm 1 and Arm 4) would be conducted to determine if celecoxib resulted in a statistically significant increase in SBP_{day}. If both the primary and secondary efficacy tests were statistically significant, a tertiary analysis would be conducted to compare Arm 1 and Arm 3 to determine if the combination drug product was superior to celecoxib monotherapy by reducing SBP_{day}.

Statistical Comments:

1. *This was not a non-inferiority study in strict sense since a placebo arm was available and the actual treatment effects of all the treatment arms in the trial were observed and could be compared directly, therefore one can directly test if the combination therapy kept at least half of the treatment effect of the amlodipine monotherapy.*

2. *Denote P, A, C, A+C as the mean changes from baseline of SBP_{day} to the study end in the placebo, amlodipine, celecoxib monotherapy, and the combination therapy, respectively. To test if the combination therapy keeps half of the treatment effect of the amlodipine monotherapy, it suffices to test if A+C < ½A, or (A+C) - ½A < 0. That can be achieved if one shows the upper limit of the 95% CI of (A+C) - ½A is below zero. Although the sponsor conducted such an analysis as a post hoc sensitivity analysis upon the Agency's request at the pre-NDA meeting, their primary efficacy analysis compared the upper limit of the 95% CI of (A+C) – A with the observed value of -½A, therefore ignored the variability of the latter. That led to unreliable conclusion. On the other hand, if the sponsor had replaced the latter with its lower 95% confidence bound to incorporate its variability, that would have been too conservative.*

3. *The statistical reviewer conducted simple and more straightforward tests of (A+C) - ½A < 0 using t-test and nonparametric methods. The results supported sponsor's conclusion that the combination therapy of amlodipine and celecoxib kept at least half of the effect of the amlodipine monotherapy.*

3.2.3 Patient Disposition

All 152 randomized patients (100%) received at least one administration of the study drugs and were therefore included in the safety population. The ITT population consisted of 150 patients (98.7% of the randomized population). One patient in the celecoxib arm and 1 patient in the placebo arm did not meet the ITT requirement for paired valid ABPM measurements and were therefore excluded from this analysis set.

Of the 152 randomized patients, 144 (94.7%) were white, 3 (2.0%) were black, 5 (3.3%) were Asian, 56 (36.8%) were female and 96 (63.2%) were male. The mean ± SD age was 56.1 ± 8.8

years (median 55.0; range 40-75). The demographic and baseline characteristics including age, gender, race, weight, BMI, respiration rate, and ECG abnormality for each treatment arm were comparable to the overall population. The baseline SBP and DBP levels were comparable across the treatment groups. In the randomized population, the mean SBP_{day} in the celecoxib group was 150.8 mmHg compared to that of 148.0 for the other three groups.

Table 3.1 Key Demographic/Baseline Characteristics by Treatment Groups (Randomization Population)

	Amlodipine + Celecoxib (N=49)	Amlodipine (N=45)	Celecoxib (N=31)	Placebo (N=27)
Age, *years* (mean ± SD)	57.7 ± 8.0	57.3 ± 9.4	54.9 ± 8.2	52.5 ± 9.1
Sex:				
Females (*N, %*)	17 (34.7%)	19 (42.2%)	10 (32.3%)	10 (37.0%)
Males (*N*, %)	32 (65.3%)	26 (57.8%)	21 (67.7%)	17 (63.0%)
Ethnic origin:				
White (*N, %*)	46 (93.9%)	43 (95.6%)	29 (93.5%)	26 (96.3%)
Black (*N*, %)	0 (0.0%)	2 (4.4%)	1 (3.2%)	0 (0.0%)
Asian (*N*, %)	3 (6.1%)	0 (0.0%)	1 (3.2%)	1 (3.7%)
Height, *cm* (mean ± SD)	171.7 ± 11.3	169.8 ± 8.9	173.9 ± 9.5	172.1 ± 10.1
Weight, *kg* (mean ± SD)	82.1 ± 17.2	84.6 ± 13.7	90.3 ± 13.6	84.8 ± 14.4
BMI, kg/m^2 (mean ± SD)	27.78 ± 3.72	29.26 ± 3.71	29.75 ± 2.96	28.52 ± 3.52
Pulse rate, *bpm* (mean ± SD)	65.6 ± 11.0	70.0 ± 9.7	67.7 ± 11.6	68.0 ± 9.6
Respiration rate, *breaths/min* (mean ± SD)	15.2 ± 2.9	15.7 ± 3.0	15.4 ± 2.9	15.3 ± 2.4
Oral body temperature, *°C* (mean ± SD)	36.33 ± 0.42	36.36 ± 0.44	36.29 ± 0.37	36.26 ± 0.48
SBP left arm, *mmHg* (mean ± SD)	151.3 ± 10.6	150.8 ± 10.1	154.8 ± 10.8	152.1 ± 11.4
SBP right arm, *mmHg* (mean ± SD)	152.3 ± 8.6	153.7 ± 11.2	157.3 ± 9.3	153.0 ± 12.5
DBP left arm, *mmHg* (mean ± SD)	90.9 ± 8.3	89.2 ± 7.3	90.8 ± 8.8	91.4 ± 8.5
DBP right arm, *mmHg* (mean ± SD)	91.9 ± 8.5	88.8 ± 7.7	91.9 ± 9.9	91.7 ± 7.9
SBP_{day}, *mmHg* (mean ± SD)	148.7 ± 7.4	147.6 ± 8.7	150.8 ± 8.9	147.3 ± 8.6
SBP_{night}, *mmHg* (mean ± SD)	126.8 ± 10.5	125.7 ± 11.7	132.1 ± 16.2	122.3 ± 10.7
SBP_{24h}, *mmHg* (mean ± SD)	141.7 ± 7	140.6 ± 8.2	144.1 ± 8.3	138.8 ± 7.5
DBP_{day}, *mmHg* (mean ± SD)	91.4 ± 8.2	88.3 ± 6.9	91.7 ± 8.9	92 ± 9
DBP_{night}, *mmHg* (mean ± SD)	75.8 ± 8.9	72.3 ± 8.1	75.7 ± 9.6	71.5 ± 10.4
DBP_{24h}, *mmHg* (mean ± SD)	86.2 ± 7	83.1 ± 6.1	85.8 ± 7.3	84.7 ± 8.3
ECG:				
Normal (*N, %*)	37 (75.5%)	36 (80.0%)	22 (71.0%)	24 (88.9%)
Abnormal NCS (*N, %*)	12 (24.5%)	9 (20.0%)	9 (29.0%)	3 (11.1%)
Abnormal CS (*N*, %)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

N = number of patients
CS = clinically significant
NCS = not clinically significant

Source: Table 4 in Clinical Study Report: Study KIT-302-03-01

Of the 152 randomized patients, 146 completed the study and 144 completed the study treatment. Three patients in the amlodipine group, 2 patients in the celecoxib group, and 1 patient in the placebo group discontinued after the randomization. Among them, 2 discontinued due to adverse events, 1 due to consent withdrawal, 1 due to protocol deviation, and 2 due to other reasons.

Table 3.2 Patient Disposition by Treatment Group (Randomization Population)

	Amlodipine + Celecoxib N=49	**Amlodipine + Placebo N=45**	**Celecoxib + Placebo N=31**	**Placebo + Placebo N= 27**	**All Patients N = 152**
No. patients who completed the study	49 (100%)	42 (93.3%)	29 (93.5%)	26 (96.3%)	146 (96.1%)
No. patients who completed treatment	48 (98%)	42 (93.3%)	29 (93.5%)	25 (92.6%)	144 (94.7%)
No. patients discontinued after randomization	0 (0.0%)	3 (6.7%)	2 (6.5%)	1 (3.7%)	6 (3.9%)
Adverse event	0 (0.0%)	2 (4.4%)	0 (0.0%)	0 (0.0%)	2 (1.3%)
Withdrawal of consent	0 (0.0%)	0 (0.0%)	1 (3.2%)	0 (0.0%)	1 (0.7%)
Lost to follow-up	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Protocol deviation	0 (0.0%)	1 (2.2%)	0 (0.0%)	0 (0.0%)	1 (0.7%)
Study termination	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Other	0 (0.0%)	0 (0.0%)	1 (3.2%)	1 (3.7%)	2 (1.3%)

Percentage (%) was calculated using the randomized set as the denominator.
Source: Table T14.1-2 in Clinical Study Report: Study KIT-302-03-01

3.2.3.1 Protocol Deviations

Protocol deviations were categorized into major and minor deviations with the criteria being detailed in the Data Review Report. The major protocol violations had three categories: completing less than 75% of the planned study drug doses, taking prohibited medication during the study, and violation of exclusion criterion 19.

According to the CSR, 11 major protocol violations were reported. A total of 8 patients (5.3%) in the randomized population had at least one major protocol violation, including 1 patient in the amlodipine + celecoxib arm, 4 in the amlodipine arm, 2 in the celecoxib arm, and 1 in the placebo arm. The most common major protocol violation of completing less than 75% of the planned study drug doses was reported in 3 patients in the amlodipine arm, 2 in the celecoxib arm, and 1 in the placebo group. Prohibited medication taken during the study was reported in 1 patient in the amlodipine + celecoxib arm, 2 in the amlodipine arm, and 1 in the celecoxib arm.

3.2.4 Results and Conclusions

Primary Efficacy Analysis

All 152 randomized patients received at least one administration of the study drugs and were therefore included in the safety population. The ITT population consisted of 150 patients, including 49 in the amlodipine + celecoxib arm, 45 in the amlodipine arm, 30 in the celecoxib arm, and 26 in the placebo arm. The primary efficacy analyses were conducted for the ITT population using LOCF for the subjects who dropped out before the end of the study.

The mean SBP_{day} at baseline, the end of study, and its change from baseline to the end of study for the ITT population are presented in Table 3.3. The mean changes of SBP_{day} ± SD from baseline to the end of study were -10.6 ± 9.2 mmHg in the amlodipine + celecoxib arm, -8.83 ± 8.13 mmHg in the amlodipine arm, -0.5 ± 8.8 mmHg in the celecoxib arm, and -2.11 ± 8.2 mmHg in the placebo arm.

Table 3.3 Mean SBP_{day} at Baseline, End of Study, and its Change from Baseline to the End of Study (ITT population)

Treatment Arm	N	Baseline Mean (SD)	End of Study Mean (SD)	Change from Baseline to End of Study Mean (SD)
Amlodipine + celecoxib	49	148.7 (7.4)	138.1 (9.8)	-10.6 ± 9.2
Amlodipine	45	147.57 (8.74)	138.74 (9.6)	-8.83 ± 8.13
Celecoxib	30	150.6 (9.0)	150.1 (10.0)	-0.5 ± 8.8
Placebo	26	147.24 (8.81)	145.13 (10.07)	-2.11 ± 8.2

N = number of patients
End of study measurement is the latest measurement available (Day 6 to Day 7 or Day 13 to Day 14)
The means are all in mmHg
Source: Table 5 in Clinical Study Report: Study KIT-302-03-01

Using the prespecified statistical analysis method, the sponsor tested the non-inferiority of the amlodipine + celecoxib over amlodipine arm, by comparing the upper limit of the 95% CI for $(A+C) - A$ with the estimated value of $-½A$. The estimated value of $(A+C) - A$ was -1.77 mmHg with the 95% CI of (-5.35, 1.81) mmHg, and the estimated value of $-½A$ was 4.41 mmHg. Since the upper limit of the CI of $(A+C) - A$ was below $-½A$, the sponsor concluded that the amlodipine + celecoxib combination therapy was statistically non-inferior to the amlodipine monotherapy.

Reviewer's Analyses

As indicated in Section 3.2.2, the statistical reviewer considered the sponsor's analysis methods problematic by ignoring the variability of $-½A$. Instead, the reviewer constructed the 95% CI for $(A+C) - ½A$ and tested the following hypothesis using both *t*- and non-parametric tests,

$$H_0: (A+C) - ½A = 0 \text{ vs. } H_A: (A+C) - ½A < 0.$$

The mean estimate of $(A+C) - ½A$ was -6.18 and the 95% CI was (-9.15, -3.21) which was below zero. So H_0 is rejected. All the nonparametric tests gave $p < 0.0001$. All these results supported the conclusion that the amlodipine + celecoxib combination therapy kept at least half the effect of the amlodipine monotherapy in treating the adult patients in the designed population. In addition, considering that the treatment effect often means the effect adjusted by placebo, the reviewer also estimated the placebo adjusted effect of each treatment arm, i.e., $(A+C) - P$ for the combination arm and $A - P$ for the amlodipine arm. The null hypothesis H_0: $[(A+C) – P] – ½ (A-P) = (A+C) - ½A - ½P = 0$ was tested. The estimated value of $(A+C) - ½A - ½P$ was -5.13 and the 95% CI was (-8.39, -1.87) mmHg, that gave a *t* value of -3.09 and *p* value of 0.001, indicating a statistically significant difference. So the placebo adjusted treatment effect also supported the conclusion that the combination therapy kept at least half of the effect of the amlodipine monotherapy.

Secondary Efficacy Analysis of the Primary Efficacy Endpoint

Per the serial testing procedure in the SAP, since the primary efficacy analysis was statistically significant, the secondary efficacy analysis of testing if celecoxib significantly increased the mean change from baseline of SBP_{day} of placebo was performed. The difference between the two mean changes was 1.58 mmHg, with the 95% CI of (-2.99, 6.15) mmHg. The *t*-test gave a non-statistically significant *p* value of 0.491. As the result, the tertiary test of the superiority of combination therapy over celecoxib was not performed.

Additional analyses on the Primary and Secondary Efficacy Endpoint

An exploratory analysis of testing the difference in the primary endpoint between Arms 1 and 4 was conducted. That gave a difference of -8.48 mmHg, with the 95% CI of (-12.79, -4.18) mmHg and $p < 0.001$, and therefore gave a supportive evidence for the superiority of amlodipine + celecoxib over placebo.

3.3 Evaluation of Safety

NA.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Subgroup Analyses

Given that only 5% of the ITT population were non-whites, exploratory subgroup analyses were not performed for race. Subgroup analyses were performed for the primary efficacy endpoint for age and gender groups in the ITT population. There were 55 women and 95 men in the population, with age ranged from 40 to 75, a mean of 56.1, and a median of 55. Since the age of 65 is used in labeling to separating patients into elderly and non-elderly, we separated the patients into two groups, from 40 to 65 and above 65, with 128 and 22 patients, respectively. The subgroup means and standard deviations for the primary endpoint in all the treatment arms are depicted in Tables 4.1 and 4.2.

The subgroup analyses show generally consistent results with the overall ITT population. For sex subgroup analyses (Table 4.1), the results suggested that women tended to be more responsive to the treatments than men in reducing SBP_{day} values. However, after adjusting for the placebo effect, the improvements were not obvious. There seemed to be little differences in the response to the treatments between elder and non-elder patients, except to the celecoxib. The elder group had an increase in the mean change of SBP_{day}. Given there were only 3 patients in the group, one cannot make any meaningful conclusion. The subgroup results must be interpreted with caution due to small number of patients in the subgroups.

Table 4.1 Subgroup Analysis for Sex: Change from Baseline in SBP_{day} (mmHg) in All Treatment Arms (ITT)

Treatment Arm	N	Baseline Mean (SD)	End of Study Mean (SD)	Change from Base to End of Study
Men				
Amlodipine + celecoxib	32	145.0 (9.2)	141.3 (10.0)	-7.8 (7.8)
Amlodipine	26	143.2 (9.9)	139.8 (8.7)	-7.0 (7.4)
Celecoxib	21	149.3 (7.6)	150.4 (11.2)	0.5 (8.1)
Placebo	16	146.1 (12.2)	145.5 (12.0)	0.2 (7.1)
Women				
Amlodipine + celecoxib	17	139.4 (8.9)	132.1 (6.0)	-15.8 (9.6)
Amlodipine	19	144.2 (9.8)	137.2 (10.8)	-11.3 (8.6)
Celecoxib	9	152.1 (8.3)	149.2 (7.2)	-2.8 (10.2)
Placebo	10	149.4 (6.0)	144.6 (6.5)	-5.8 (8.8)

Table 4.2 Subgroup Analysis for Age Groups: Age ≤ 65 vs. Age > 65 Change from Baseline in SBP_{day} (mmHg) in Treatment Arms (ITT)

Treatment Arm	N	Baseline Mean (SD)	End of Study Mean (SD)	Change from Base to End of Study
Age ≤ 65				
Amlodipine + celecoxib	41	144.4 (9.3)	138.9 (10.2)	-10.5 (9.9)
Amlodipine	36	143.8 (10.3)	139.1 (10.1)	-8.5 (7.5)
Celecoxib	27	149.7 (7.5)	149.0 (9.7)	-1.2 (8.8)
Placebo	24	147.0 (10.5)	145.7 (10.2)	-2.1 (8.5)
Age > 65				
Amlodipine + celecoxib	8	136.3 (6.3)	133.7 (6.0)	-11.1 (4.8)
Amlodipine	9	143.0 (7.5)	137.2 (7.7)	-10.0 (10.6)
Celecoxib	3	153.9 (10.8)	160.0 (8.1)	5.7 (6.3)
Placebo	2	151.3 (8.4)	138.5 (7.1)	-2.5 (2.8)

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

NA

5.2 Collective Evidence

The pivotal study KIT-302 was a multi-center, randomized, double-blind, placebo-controlled trial to evaluate the effect of celecoxib on the efficacy and safety of amlodipine and to evaluate PK drug-drug interactions in subjects with hypertension requiring antihypertensive therapy. The sponsor provided high quality data sets along with the programs that allowed the statistical reviewer to duplicate the efficacy results they submitted. The primary efficacy analyses were conducted in the ITT population.

The sponsor used a problematic statistical method to conduct the primary efficacy comparison and ignored the variability of the estimated mean change of SBP_{day} in the amlodipine therapy in the analyses. The statistical reviewer corrected their method and provided a valid test. The new analyses supported the conclusion that combination therapy retained at least half the effect of amlodipine on systolic daytime blood pressure.

5.3 Conclusions and Recommendations

In this NDA, the sponsor submitted a multi-center, randomized, double-blind, placebo-controlled study to support the effectiveness of celecoxib on the efficacy and safety of amlodipine in subjects with hypertension requiring antihypertensive therapy.

With a total of 152 randomized patients received at least one administration of the study drugs and 150 in the ITT population, the primary efficacy analysis of the pivotal study KIT-302 indicated that combination therapy retained at least half the effect of the amlodipine monotherapy on systolic daytime blood pressure. The secondary comparison of the primary endpoint between the celecoxib and placebo arm yielded a numerical difference in favor of the placebo. But the difference was not statistically significant to support that the celecoxib monotherapy gave less reduction in the systolic daytime blood pressure than placebo.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

FANHUI KONG
04/10/2018

HSIEN MING J HUNG
04/10/2018