CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

210045Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Office of Clinical Pharmacology Review

NDA Number	210045
Link to EDR	\\cdsesub1\evsprod\nda210045
Submission Date	7/31/2017
Submission Type	Standard review
Brand Name	Consensi®
Generic Name	Celecoxib and Amlodipine Besylate tablets
Dosage Form and Strength	Fixed dose combination of Celecoxib / Amlodipine Besylate tablets: 200 mg/2.5 mg, 200 mg/5 mg and 200 mg/10 mg
Route of Administration	Oral
Proposed Indication	Patients who require (b) (4) treatment (b) (4) of osteoarthritis and who also require the treatment of hypertension, to lower blood pressure
Applicant	Kitov Pharmaceuticals
Associated IND	IND112830
OCP Review Team	Venkateswaran Chithambaram Pillai, MS(Pharm), PhD; Sudharshan Hariharan, PhD

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1. EXECUTIVE SUMMARY

Kitov Pharmaceuticals is seeking approval for a fixed dose combination (FDC) product consisting of amlodipine besylate, a calcium channel blocker and celecoxib, a non-steroidal anti-inflammatory drug (NSAID) via 505(b)(2) new drug application. The proposed indication is for patients who require [redacted] (b) (4) of osteoarthritis and who also require the treatment of hypertension. This product is developed as a convenience formulation to facilitate and improve patient compliance when its individual components are administered together once a day. Because of its proposed use as a convenience formulation, the clinical review recommends approval of this product [redacted] (b) (4) for patients for whom treatment with both amlodipine for hypertension and celecoxib for osteoarthritis are appropriate (refer Clinical Review by Dr. Tsu-Yun McDowell, 04/23/2018). The proposed FDC product is available in three different strengths, amlodipine besylate/celecoxib: 2.5 mg/200 mg (low strength), 5 mg/200 mg (intermediate strength) and 10 mg/200 mg (high strength). The application relies on the Agency's previous finding of safety and efficacy of the reference listed drugs (RLDs), Norvasc® (amlodipine besylate; NDA019787) tablets and Celebrex® (celecoxib; NDA020998) capsules.

In earlier interactions with the Agency, the Applicant was informed that their development program for this FDC should address the following – (i) establishing a pharmacokinetic (PK) bridge between FDC and individual RLDs; (ii) characterizing the impact of food on FDC; and (iii) characterizing any PK and pharmacodynamic (PD) interactions between the components of the FDC. In support of the PK bridge, the Applicant submitted three relative bioavailability (BA) studies that compared the PK of amlodipine and celecoxib between FDC and free combination at high strength (fasting), high strength (fed) and low strength (fasting and fed). Because the proposed strengths of the FDC product were not compositionally proportional, the Agency recommended the Applicant to conduct BA studies for the low and high strength FDC tablets. The effect of food was also characterized in these relative BA studies. The Applicant also conducted a clinical PK and PD drug interaction study in patients with newly diagnosed hypertension. This study assessed the effects on blood pressure by comparing the reduction in mean change from baseline for day time ambulatory systolic blood pressure on day 14 between a free combination of 10 mg amlodipine besylate and 200 mg celecoxib RLDs and individual RLDs, either 10 mg amlodipine besylate or 200 mg celecoxib. The PD interaction on analgesic effect of celecoxib was not evaluated because the Agency agreed to waive this assessment in the context that the proposed FDC is a convenience product for substitution with no new safety or efficacy claims and the low likelihood of an interaction (Consult response by Dr. Hariadi, DARRTS date: 04/01/2016).

This review primarily addresses (i) PK bridging for celecoxib and amlodipine between FDC product and individual RLDs in healthy subjects, (ii) effect of food on FDC, and (iii) clinical PK and PD interaction between amlodipine and celecoxib. Please refer to section 1.3 for Key Clinical Pharmacology Findings.

1.1 Recommendations

The Office of Clinical Pharmacology (OCP/DCP I) finds the PK bridging between the FDC and RLDs to be acceptable and the blood pressure response of the combination treatment to be non-inferior to amlodipine treatment alone. Based on these findings, the review team recommends the approval of amlodipine besylate/celecoxib FDC tablet for use in patients in whom treatment with these agents are appropriate for hypertension and osteoarthritis, respectively.

1.2 Post-Marketing Requirements and Commitments

None

1.3 Key Clinical Pharmacology Findings

- Amlodipine besylate / celecoxib FDC tablet at high strength (10 mg/200 mg) [Test] is bioequivalent to free combination of amlodipine (10 mg) and celecoxib (200 mg) [Reference] under fasted and fed conditions.
- Amlodipine besylate / celecoxib FDC tablet at low strength (2.5 mg/200 mg) [Test] is bioequivalent to free combination of amlodipine (2.5 mg) and celecoxib (200 mg) [Reference] under fasted condition.
- Following administration of low strength FDC under fasted and fed condition, food did not affect the exposures of amlodipine but increased C_{max} and $AUC_{0-\infty}$ of celecoxib by approximately 86% and 26%, respectively. However, because of the FDC and free combination is bioequivalent for celecoxib under fed conditions, no specific instructions to food is necessary, as recommended in Celebrex® PI.
- Clinical PK and PD interaction study in patients with newly diagnosed hypertension showed approximately 30% lower exposures for amlodipine in the combination group compared to Norvasc®. However, the effect on systolic blood pressure of the combination treatment was non-inferior to amlodipine alone. The exposures of celecoxib were not altered between the combination group and Celebrex®.

2. SUMMARY OF CLINICAL PHARMACOLOGY ASSESSMENT

2.1 Dosing and Therapeutic Individualization

2.1.1 General dosing

The recommended starting dose of amlodipine besylate / celecoxib FDC tablet for oral administration is 5 mg/200 mg once daily, and the maximum dose is 10 mg/200 mg once daily for adult patients who require (b) (4) treatment for osteoarthritis and hypertension and for which treatment with celecoxib and amlodipine are appropriate. Initiate at 2.5 mg/200 mg when adding amlodipine/celecoxib FDC tablet to other anti-hypertensive therapy. The doses of this FDC should be adjusted based on blood pressure goals.

Celecoxib should be used at the lowest effective dosage. If a daily dosage of celecoxib other than 200 mg is indicated or administration of celecoxib as a divided dose (100 mg twice a day) is desired, individual components should be used rather than amlodipine/celecoxib FDC tablet.

2.1.2 Therapeutic individualization

Elderly patients: Initiate at 2.5 mg/200 mg amlodipine/celecoxib FDC tablet. Adjust the dose based on blood pressure goals.

Hepatic Impairment: In patients with moderate hepatic impairment (Child-Pugh Class B), the dose of celecoxib should be reduced by 50%. Because amlodipine/celecoxib FDC tablet is not available in lower strengths of celecoxib, dosing with the individual components should be considered for these patients. The use of celecoxib, including amlodipine/celecoxib FDC tablet in patients with severe hepatic impairment is not recommended.

Poor Metabolizers of CYP2C9 Substrates: In patients who are known or suspected to be poor cytochrome P450 (CYP) 2C9 metabolizers based on genotype or previous history/experience with other CYP2C9 substrates (such as warfarin, phenytoin), treatment should be initiated with half of the lowest recommended dose of celecoxib. Because amlodipine/celecoxib FDC tablet is not available in lower strengths of celecoxib, dosing with the individual components should be considered for these patients.

2.2 Outstanding Issues

None.

3. COMPREHENSIVE CLINICAL PHARMACOLOGY REVIEW

3.1 Overview of the Product and Regulatory Background

Consensi®, a fixed dose combination of celecoxib, an NSAID, and amlodipine besylate, a calcium channel blocker is proposed for treatment of patients with osteoarthritis and hypertension. This FDC tablet is being developed as a convenience formulation to facilitate and improve patient compliance when its individual components are administered together once a day.

Kitov Pharmaceuticals submitted a request for Special Protocol Assessment for the clinical PK and PD interaction study under IND112830. The protocol was agreed upon by the Agency. In 2016, a pre-NDA meeting was held to obtain concurrence with the Agency that the application's contents will meet FDA requirements for the NDA filing. The Agency agreed with the Sponsor's intention to submit new drug application via 505(b)(2) pathway that relies on Agency's previous findings of safety and efficacy from NDA 019787 for Norvasc® (amlodipine besylate) tablets and NDA 020998 for Celebrex® (celecoxib) capsules as the reference listed drugs.

3.2 General Pharmacology and Pharmacokinetic Characteristics

Pharmacology	
Mechanism of action	Amlodipine: Amlodipine is a dihydropyridine calcium channel antagonist (calcium ion antagonist or slow-channel blocker) that inhibits the transmembrane influx of calcium ions into vascular smooth muscle and cardiac muscle. Thus, it reduces peripheral vascular resistance and blood pressure. Celecoxib: Celecoxib inhibits prostaglandin synthesis through inhibition of cyclooxygenase-2. It exerts analgesic, anti-pyretic and anti-inflammatory activities.
Pharmacokinetics	
Absorption	Amlodipine: Following a single oral administration of amlodipine/celecoxib (2.5 mg/200 mg or 10 mg/200 mg) FDC tablets under fasted conditions, C_{max} was achieved within 8 h for amlodipine and 2 h for celecoxib. The rate and extent of absorption of amlodipine and celecoxib following administration of FDC tablet were similar to when the individual components were taken together. Upon administration of amlodipine/celecoxib (2.5 mg/200 mg) tablet along with high fat meal, food has no influence on C_{max} and AUC of amlodipine however time to C_{max} (T_{max}) was delayed from 8 to 10 h. Food increases C_{max} by 86% and AUC by 25.5%, and delays T_{max} from 2 to 3.1 h.

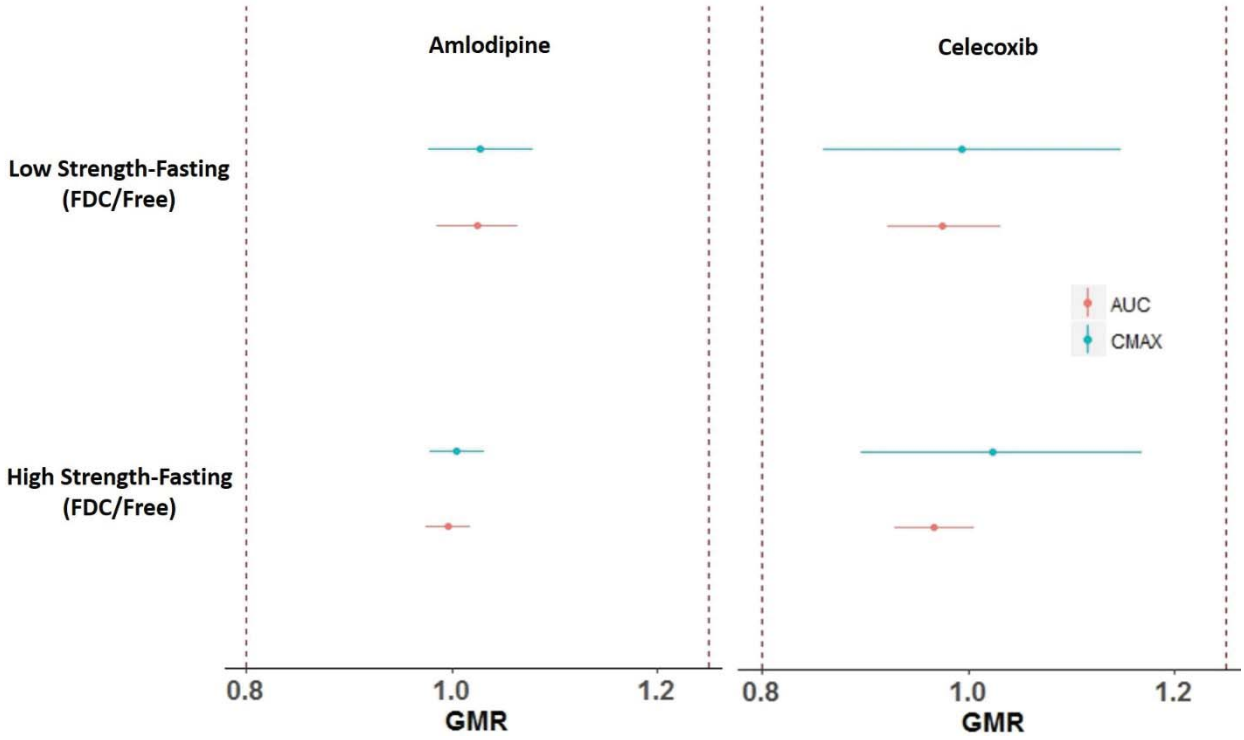
Distribution	Protein binding of amlodipine and celecoxib is 97% and 93%, respectively. Volume of distribution of amlodipine and celecoxib is ~400 L and 18 L, respectively.
Metabolism	Amlodipine is extensively (90%) metabolized in the liver to inactive metabolites via CYP3A4. Celecoxib is primarily metabolized by CYP2C9 to inactive metabolites. In vitro studies indicate that celecoxib is not an inhibitor of CYP3A4.
Excretion	Approximately 10% of amlodipine and 60% of its metabolites are excreted into urine. The terminal elimination half-life ($t_{1/2}$) of amlodipine ranges from 30 to 50 h. Less than 3% of unchanged celecoxib is excreted into urine. Approximately 57% of the administered radiolabeled celecoxib was excreted into feces and 27% excreted into urine. The effective $t_{1/2}$ of celecoxib is approximately 11 hours. The apparent plasma clearance (CL/F) of celecoxib is about 500 mL/min.

3.3 Clinical Pharmacology Review Questions

3.3.1 Is there an appropriate PK bridge for amlodipine and celecoxib between the FDC and individual reference products?

Pharmacokinetics of both high strength (10 mg amlodipine/200 mg celecoxib) and low strength (2.5 mg amlodipine/200 mg celecoxib) FDC tablets (test product) were compared to free combination of amlodipine and celecoxib reference products at corresponding low and high strengths under fasting condition in healthy subjects. Both C_{max} and AUC of amlodipine and celecoxib are bioequivalent between FDC and free combination at high and low strengths (Figure 1). Between subject variability in C_{max} and AUC of amlodipine and celecoxib are also similar between FDC and free combination at high and low strengths. These results establish a pharmacokinetic bridge for the proposed amlodipine/celecoxib FDC tablet to the reference products.

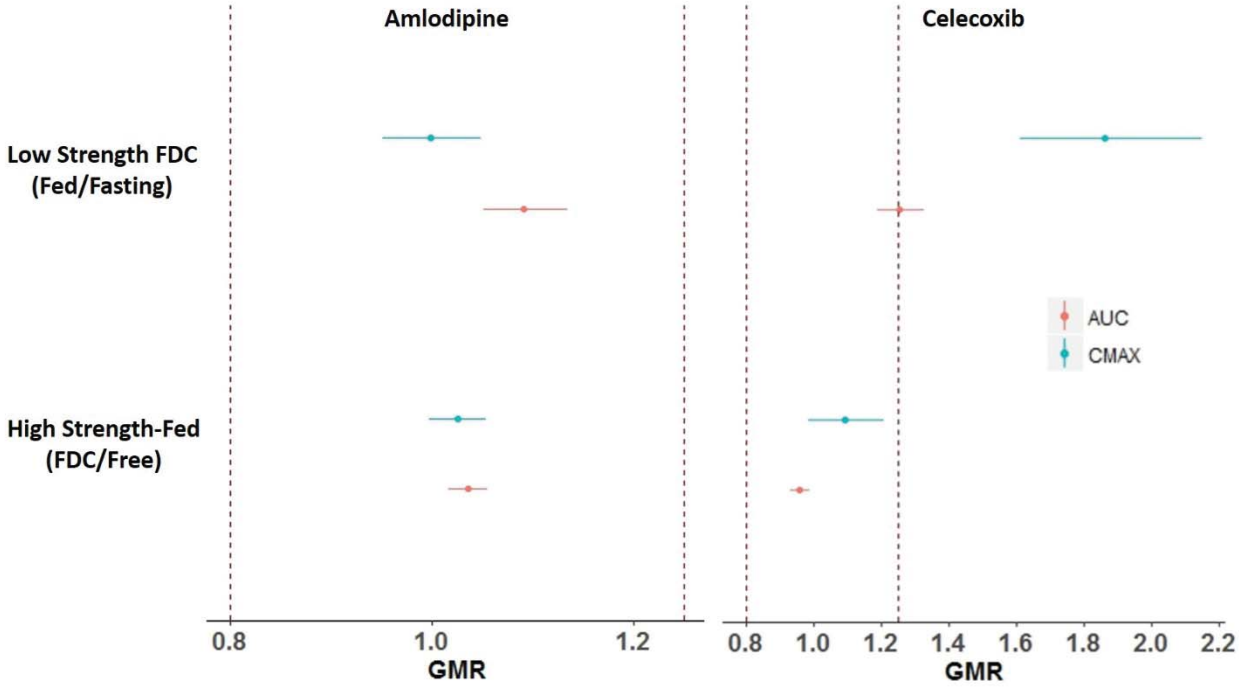
Figure 1 shows the geometric mean ratio (GMR) and 90% CI for amlodipine and celecoxib following comparison of low strength and high strength FDC of test product and free combination of reference products under fasting condition.



3.3.2 What is the effect of food on the exposures of amlodipine and celecoxib in the FDC? Does this product require specific dosing instruction with regard to food in the product insert?

The effect of food on the PK of low strength FDC tablet was evaluated in healthy subjects. Food did not influence the C_{max} and $AUC_{0\text{-}72h}$ of amlodipine but increased the C_{max} of celecoxib by 86% and $AUC_{0\text{-}\infty}$ by 26% (Figure 2). Food delayed the T_{max} of amlodipine and celecoxib from 8 h to 10 h and 2 h to 3 h, respectively. While food showed an impact on the exposures of celecoxib with the FDC, the exposures to celecoxib in a fed condition was bioequivalent between FDC (at high strength) and free combination of RLDs. This suggests that any impact of food on celecoxib is reasonably similar between the FDC and the RLD. Since, Celebrex® USPI allows the use of celecoxib with or without food, (b) (4)

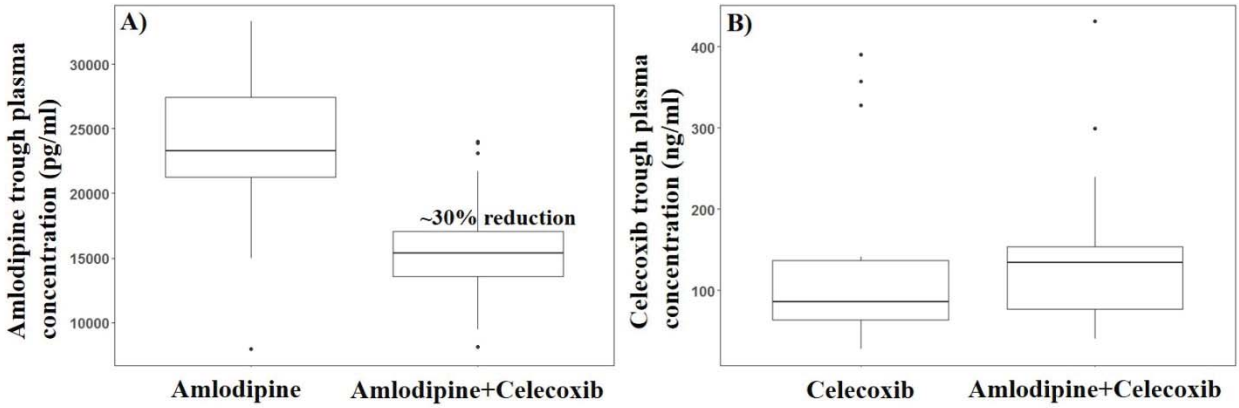
Figure 2 represents the GMR and 90% CI for amlodipine and celecoxib following administration of low strength FDC under fed and fasting condition, and comparison of high strength FDC of test product and free combination of reference products under fed condition.



3.3.3 Is there any PK drug interaction between the components of the FDC?

On the basis of ADME features of celecoxib and amlodipine (please refer to Section 3.2), a significant pharmacokinetic drug interaction is not expected. Hence, a dedicated drug interaction study was not warranted and the Applicant was allowed to evaluate this interaction in the pharmacodynamic study. In Study KIT-302-03-01 (please refer to section 4.2 for more details), the pharmacokinetic interaction was assessed by collecting trough samples (24 h post-dose) in a subset of patients (N=70) on day 14. The trough concentrations of amlodipine were lower by approximately 30% in the combination group compared to amlodipine administered alone (Figure 3). The trough concentrations of celecoxib were similar between combination and celecoxib alone treatment. The reduced exposures to amlodipine observed in this study should be interpreted with caveats about the design (parallel versus crossover), sample collection (a single-point estimation of exposures versus rich sample collection) and the lack of any expectation for a metabolic interaction.

Figure 3 shows the comparison of amlodipine (A) and celecoxib (B) steady state plasma trough concentrations (24 h post-dose) between amlodipine or celecoxib treatment alone and amlodipine + celecoxib combination treatment in patients with hypertension.



3.3.4 Is there any pharmacodynamic interaction between the components of the FDC with regard to blood pressure?

The pharmacodynamic interaction with regard to blood pressure lowering effect of amlodipine was assessed in a prospective, randomized, double-blind, placebo-controlled, multi-center study (KIT-302-03-01) in adults with newly diagnosed hypertension. The study was conducted in 11 centers in the United Kingdom. A total of 152 patients were enrolled in this study. These patients were randomized (1.5:1.5:1:1) to receive:

Arm 1: over-encapsulated (OE) Norvasc® 10 mg + Celebrex® 200 mg (N=49)
Arm 2: OE Norvasc® 10 mg + matched placebo for Celebrex® (N=45)
Arm 3: OE Celebrex® 200 mg + matched placebo for Norvasc® (N=31)
Arm 4: matched placebo for Norvasc® + matched placebo for Celebrex® (N=27)

These treatments were administered once daily for a total of 14 days. Treatments were over-encapsulated to maintain blinding. Dissolution of amlodipine and celecoxib was similar between OE capsules and RLDs. To evaluate the blood pressure effects of celecoxib, a celecoxib alone treatment arm was studied. Placebo group was included to allow assessment of a placebo corrected treatment effect for the FDC and celecoxib alone treatment groups. To rule out a pharmacodynamic interaction, the Applicant had to show that at least 50% of the blood pressure lowering effect of amlodipine was preserved with the FDC. Therefore, the primary endpoint, as proposed by the Applicant, was the upper bound of the 95% CI of the mean difference in ambulatory SBP_{day} between combination treatment and amlodipine alone to be less than 50% of the mean treatment response of amlodipine alone.

The results showing average (±SD) reduction in ambulatory SBP_{day} for each of the treatment arms is shown in Table 1. As per the Applicant, the study met its primary endpoint i.e., the

upper 95% CI of the difference in SBP_{day}: -1.77 mmHg (-5.35 to 1.81) was less than 50% of the mean effect of amlodipine (4.41 mmHg). However, per the statistical review, this comparison does not consider the variability around the treatment response of amlodipine. Therefore, a sensitivity analysis was performed, where the mean difference (and 95% CI) between the combination therapy and ½ of amlodipine's treatment effect was computed. This yielded a mean difference of -6.18 mmHg with a 95% CI of -9.15 to -3.21 mmHg. Since the upper bound of the 95% CI was less than zero, this study was considered to have met its primary endpoint (please refer to Statistical Review by Dr. Fanhui Kong, 04/10/2018).

While the study met the primary endpoint, the FDC seemed to show a greater reduction in blood pressure, at least numerically, compared to amlodipine alone. This was an interesting observation, given that the exposure to amlodipine was approximately 30% lower in the FDC. It should be noted that this difference is not statistically significant [SBP_{day}: -1.77 mmHg (-5.35 to 1.81 mmHg)]. The Applicant hypothesizes that both celecoxib and amlodipine may have an independent effect on renal function thereby showing a synergistic response when administered together. However, there does not seem to be any data supporting this hypothesis from the current submission (please to refer Clinical Review by Dr. Tsu-Yun McDowell, 04/23/2018). This difference is also not statistically significant [SBP_{day}: -1.77 mmHg (-5.35 to 1.81 mmHg)] and could well be a chance finding.

Table 1. Mean SBP_{day} at Baseline, End of Study and Change from Baseline (ITT population)

Treatment Arm	N	Systolic BP, Day		
		Baseline	End of study (Day 14)	Change from baseline to End of study
Amlodipine + Celecoxib	49	148.7 ± 7.4	138.1 ± 9.8	-10.6 ± 9.2
Amlodipine	45	147.6 ± 8.7	138.7 ± 9.6	-8.8 ± 8.1
Celecoxib	30	150.6 ± 9.0	150.1 ± 10.0	-0.5 ± 8.8
Placebo	26	147.2 ± 8.8	145.1 ± 10.1	-2.1 ± 8.2

Values represent mean ± SD
Intent-to-treat (ITT) population

4. APPENDICES

This section includes information on – (a) bioanalytical method validation and performance supporting all pharmacokinetic studies, and (b) brief description of study design and detailed pharmacokinetic and pharmacodynamic results from the studies submitted in this application.

4.1 Summary of Bioanalytical Method Validation and Performance

Plasma concentrations of amlodipine and celecoxib were measured by validated liquid chromatography-tandem mass spectrometry (LC-MS/MS) assay. It was found that:

- The precision and accuracy values (Table 2) of at least two-thirds of the overall QC samples from the supporting bioanalytical reports were within ±15% (±20% at the LLOQ).
- Amlodipine and celecoxib were found to be stable in plasma after at least three freeze-thaw cycles at -20˚ C, at room temperature in human plasma over at least 24 h (short-term), at -20˚ C storage in human plasma over at least 83 days (long term) and at auto-sampler storage at 4˚ C for at least 113 h.
- The QC sample accounting for dilution showed an acceptable precision (<8%) and bias (<3.5%). The carry over effects were negligible for amlodipine and minimal but not significant for celecoxib.
- More than two-thirds of the incurred sample reanalysis (ISR) fell within 20% deviation.

The bioanalytical methods satisfy the criteria for 'method validation' and 'application to routine analysis' set by the 'Guidance for Industry: Bioanalytical Method Development', and is acceptable.

Note: Bioanalysis of amlodipine and celecoxib were performed at (b) (4) Because approval of the amlodipine/celecoxib FDC tablet relies on bridging PK to individual RLDs, relative BA studies (b) (4)-P6-039, (b) (4)-P6-127 and (b) (4)-P7-108, were considered important. Therefore, OCP requested a routine inspection of the bioanalytical site of these studies via Office of Study Integrity and Surveillance (OSIS) on (b) (4) However, OSIS recommended accepting data without an on-site inspection because the bioanalytical site was recently inspected and the results of the inspection revealed no issues (NDA210045, Bioequivalence Establishment Inspection Report Review, DARRTS, (b) (4)).

Table 2. Summary of bioanalytical methods and validation in each clinical study

Sponsor's study no	Bioanalytical study no	Facility	Analytical method	Analyte	Sample volume	Analytical range (ng/ml)	Precision (CV %)	Accuracy (%)
(b) (4) P6-039	(b) (4) P6-039	(b) (4)	LC-MS/MS	Amlodipine	100 µl	0.05-15	≤12.4%	98.0-115.1
	P6-039			Celecoxib	100 µl	3-2400	≤8.3%	98.6-106.1
P6-127	(b) (4) P6-127		LC-MS/MS	Amlodipine	100 µl	0.05-15	≤12.4%	98.0-115.1
	-P6-127			Celecoxib	100 µl	3-2400	≤8.3%	98.6-106.1
P7-108	(b) (4) P7-108		LC-MS/MS	Amlodipine	100 µl	0.05-15	≤12.4%	98.0-115.1
	-P7-108			Celecoxib	100 µl	3-2400	≤8.3%	98.6-106.1
KIT-302-03-01	(b) (4) 13575-02		LC-MS/MS	Amlodipine	200 µl	0.05-10	≤14.4%	92.0-101.6
	13575-01			Celecoxib	100 µl	10-2500	≤8.2%	96.1-106.7

4.2 Clinical PK and/or PD Assessments

A) Study (b) (4)-P6-039: Relative bioavailability of a high strength (amlodipine 10 mg / celecoxib 200 mg) FDC tablet and free combination of amlodipine (10 mg) + celecoxib (200 mg) reference products under fasting condition

This relative bioavailability study was conducted to evaluate whether the pharmacokinetics of amlodipine (10 mg)/celecoxib (200 mg) FDC tablet formulation (test) is similar to that of free combination of amlodipine besylate tablet and celecoxib (200 mg) reference products in healthy adults under fasting condition.

This was a single center, randomized, single dose, laboratory-blinded, two treatment, two period crossover study in healthy adults. A total of 40 subjects were randomized to treatment period sequence 1/2 or 2/1 (20 subjects per sequence).

Sample size was determined based on the intra-subject variability following a single dose of celecoxib (28% for C_{max} and 13% for AUC). The lowest number of subjects required to meet the Test to Reference ratio of geometric LS means within 95 and 105%, and 90% CI within 80 to 125% bioequivalence criteria with at least 80% power was about 32. Considering the drop-outs and variability around intra-subject CV estimate, 40 subjects were enrolled in the study. One subject was withdrawn for safety reasons and two subjects withdrew their informed consents due to personal reasons. The remaining 37 subjects completed the study and were included in pharmacokinetic evaluation.

Treatment 1 (Test): a single oral amlodipine (10 mg) / celecoxib (200 mg) FDC tablet under fasting condition

Treatment 2 (Reference): a single oral dose of amlodipine (10 mg) and celecoxib (200 mg) reference products administered concomitantly under fasting condition

The wash-out period between treatments is 21 days. Plasma concentrations of amlodipine and celecoxib were quantified.

Figure 4 shows the mean plasma concentration-time profile of amlodipine and celecoxib following single oral administration of FDC and free combination of amlodipine (10 mg) and celecoxib (200 mg) in healthy subjects under fasting condition.

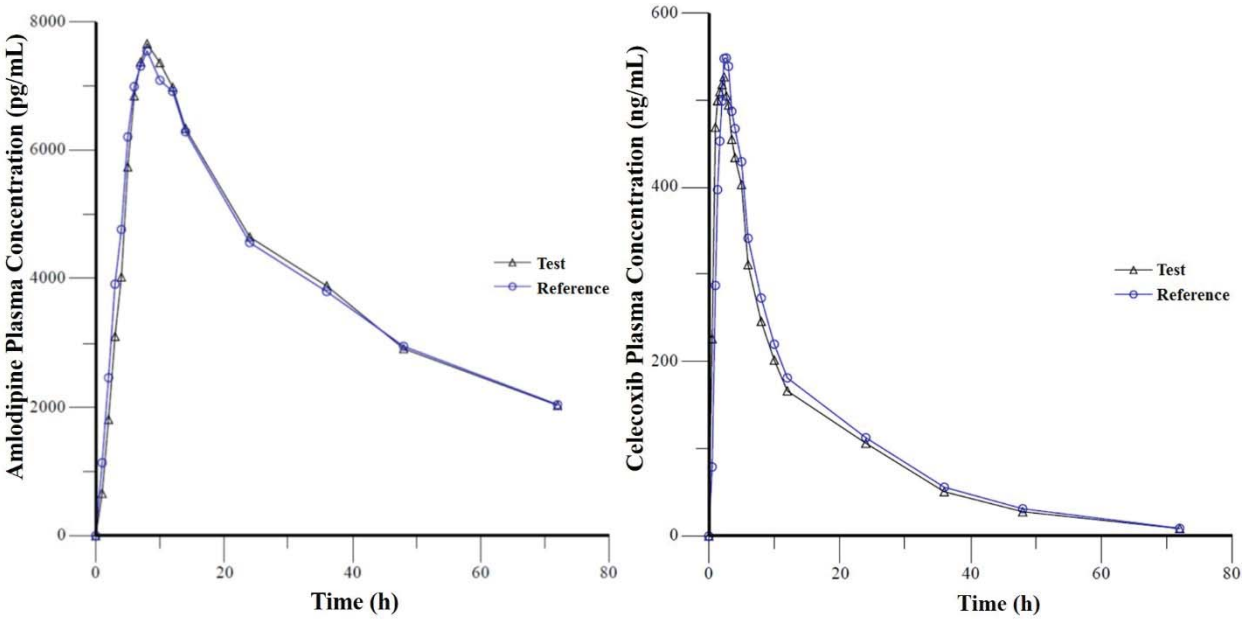


Table 3 shows the pharmacokinetic parameters and GMR (90% CI) of amlodipine and celecoxib following single oral administration of FDC (T) and free combination of amlodipine (10 mg) and celecoxib (200 mg) (R) under fasting condition

Amlodipine			
Parameter	**FDC [Test (T)] N = 37**	**Free combination [Reference (R)] N = 37**	**Geometric mean ratio [T/R] (90% CI)**
$AUC_{0\text{-}72\ h}$ (pg*h/mL)	273123 (27)	274398 (27)	100 (98-102)
C_{max} (pg/mL)	7655 (26)	7627 (25)	100 (98-103)
t_{max}@ (h)	8.0 (6.0-12.0)	8.0 (6.0-14.0)	-
Celecoxib			
Parameter	**FDC [Test (T)] N = 37**	**Free combination [Reference (R)] N = 37**	**Geometric mean ratio [T/R] (90% CI)**
$AUC_{0\text{-}72\ h}$ (ng*h/mL)	6768 (45)	7082 (44)	96 (92-100)
$AUC_{0\text{-}inf}$ (ng*h/mL)	7010 (48)	7284 (45)	97 (93-101)
C_{max} (ng/mL)	631 (57)	623 (57)	102 (90-117)

t_{max}@ (h)	2.0 (1.0-6.0)	2.3 (1.0-6.0)	-
$t_{1/2}$# (h)	12.2 (44)	11.5 (37)	-

Values represent geometric mean (% CV); @ indicates median (range); # indicate values in arithmetic mean (%CV)

B) Study (b) (4)-P6-127: Relative bioavailability of a high strength (amlodipine 10 mg / celecoxib 200 mg) FDC tablet and free combination of amlodipine (10 mg) + celecoxib (200 mg) reference products under fed condition

This relative bioavailability study was conducted to evaluate whether the pharmacokinetics of amlodipine (10 mg)/celecoxib (200 mg) FDC tablet formulation (test) is similar to that of free combination of amlodipine besylate tablet and celecoxib (200 mg) reference products in healthy adults under fed condition.

This was a single center, randomized, single dose, laboratory-blinded, two treatment, two period crossover study in healthy adults. A total of 36 subjects were randomized to treatment period sequence 1/2 or 2/1 (18 subjects per sequence).

Sample size was determined based on the intra-subject variability following a single dose of celecoxib (28% for C_{max} and 13% for AUC). The lowest number of subjects required to meet the Test to Reference ratio of geometric LSmeans within 95 and 105%, and 90% CI within 80 to 125% bioequivalence criteria with at least 80% power was about 32. Considering the drop-outs and variability around intra-subject CV, 36 subjects were enrolled in the study. All 36 subjects completed the study and were included in pharmacokinetic evaluation.

Treatment 1 (Test): a single oral amlodipine (10 mg) / celecoxib (200 mg) FDC tablet under fed condition

Treatment 2 (Reference): a single oral dose of amlodipine (10 mg) and celecoxib (200 mg) reference products administered concomitantly under fed condition

The wash-out period between treatments is 21 days. Plasma concentrations of amlodipine and celecoxib were quantified. The composition of standardized high fat, high calorie diet is shown in the following table below.

Table 4 Composition of high fat, high calorie diet

Ingredients	Amount (g)	Energy (kcal)	Protein (kcal)	Fat (kcal)	Carbohydrate (kcal)
240 mL of whole milk	29	156	36	72	48
2 large eggs	24	146	48	90	8
4 ounces of hash brown potatoes/2 patties	52	288	8	144	136
2 slices of toast	46	194	32	18	144
2 x 4.5 g of butter	7	63	0	63	0
2 strips of bacon	21	164	20	144	0
TOTAL	179	1011	144	531	336
PERCENTAGE	--	--	14.2%	52.5%	33.2%

Figure 5 shows the mean plasma concentration-time profile of amlodipine and celecoxib following single oral administration of FDC and free combination of amlodipine (10 mg) and celecoxib (200 mg) in healthy subjects under fed condition.

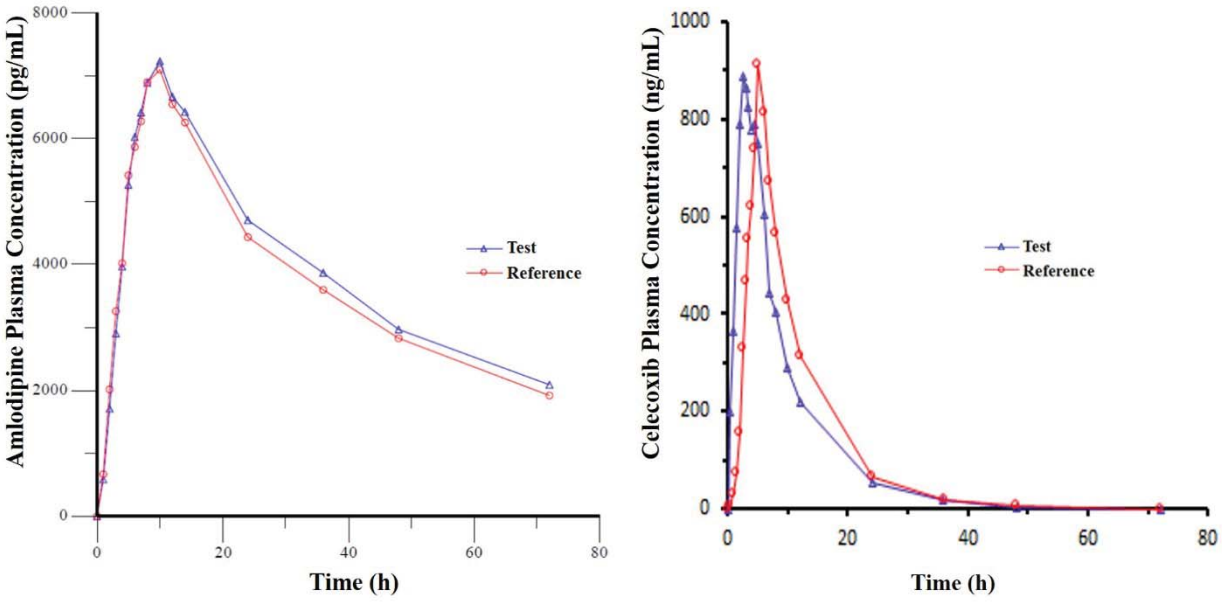


Table 5 shows the pharmacokinetic parameters and GMR (90% CI) of amlodipine and celecoxib following single oral administration of FDC (T) and free combination of amlodipine (10 mg) and celecoxib (200 mg) (R) under fed condition

Amlodipine			
Parameter	**FDC [Test (T)] N = 36**	**Free combination [Reference (R)] N = 36**	**Geometric mean ratio [T/R] (90% CI)**
$AUC_{0\text{-}72\ h}$ (pg*h/mL)	267859 (29)	258652 (27)	104 (102-106)
C_{max} (pg/mL)	7331 (29)	7155 (29)	102 (100-105)
t_{max}@ (h)	10.0 (5.0-14.0)	9.0 (5.0-14.0)	-
Celecoxib			
Parameter	**FDC [Test (T)] N = 36**	**Free combination [Reference (R)] N = 36**	**Geometric mean ratio [T/R] (90% CI)**
$AUC_{0\text{-}72\ h}$ (ng*h/mL)	7955 (30)	8298 (32)	96 (93-99)
$AUC_{0\text{-}inf}$ (ng*h/mL)	8026 (30)	8377 (31)	96 (93-99)

C_{max} (ng/mL)	1325 (35)	1213 (29)	109 (97-121)
t_{max}@ (h)	3.0 (0.5-10)	5.0 (2.5-10.0)	-
$t_{1/2}$# (h)	6.4 (24)	6.3 (25)	-

Values represent geometric mean (% CV); @ indicates median (range); # indicate values in arithmetic mean (%CV). One of the subjects from celecoxib treatment was excluded from analysis due to atypical concentration-time profile.

Reviewer Comment: *The peak concentration values for celecoxib may seem to be different if one compares the values in Table 5 to Figure 5. However, it should be noted that Figure 5 represents time-averaged plasma concentrations and Table 5 reports a geometric mean of the C_{max} observed in individual subjects.*

C) Study (b) (4)-P7-108: Relative bioavailability of a low strength (amlodipine 2.5 mg / celecoxib 200 mg) FDC tablet and free combination of amlodipine (10 mg) + celecoxib (200 mg) reference products under fasting / fed condition

This relative bioavailability study was conducted to evaluate whether the pharmacokinetics of amlodipine (2.5 mg)/celecoxib (200 mg) FDC tablet formulation (test) is similar to that of free combination of amlodipine besylate tablet and celecoxib (200 mg) reference products in healthy adults under fasting condition. This study was also aimed to evaluate the effect of food on the pharmacokinetics of amlodipine (2.5 mg)/celecoxib (200 mg) FDC tablet formulation in healthy adults.

This was a single center, randomized, single dose, laboratory-blinded, three treatment, three period crossover study in healthy adults. A total of 21 subjects were randomized to treatment period sequence 1/2/3 or 2/3/1 or 3/1/2 (7 subjects per sequence).

Sample size was determined based on the intra-subject variability following a single dose of celecoxib (28% for C_{max} and 13% for AUC). The lowest number of subjects required to meet the Test to Reference ratio of geometric LSmeans within 95 and 105%, and 90% CI within 80 to 125% bioequivalence criteria with at least 80% power was about 32. Considering the drop-outs and variability around intra-subject CV, 21 subjects were enrolled in the study. All 21 subjects completed the study and were included in pharmacokinetic evaluation.

Treatment 1 (Test 1): a single oral amlodipine (2.5 mg) / celecoxib (200 mg) FDC tablet administered with 240 mL water following a 10 h overnight fast

Treatment 2 (Reference): a single oral dose of amlodipine (2.5 mg) and celecoxib (200 mg) reference products administered with 240 mL water following a 10 h overnight fast

Treatment 3 (Test 2): a single oral dose of amlodipine (2.5 mg) / celecoxib (200 mg) FDC tablet administered with 240 mL water following a 10 h overnight fast and 30 min after the start of a high fat, high calorie breakfast.

The wash-out period between treatments is 21 days. Plasma concentrations of amlodipine and celecoxib were quantified. The composition of standardized high fat, high calorie diet is similar to that described under study (b) (4)-P6-127.

Figure 6 shows the average plasma concentration-time profile of amlodipine and celecoxib following single oral administration of FDC and free combination of amlodipine (2.5 mg) and celecoxib (200 mg) in healthy subjects under fasting condition.

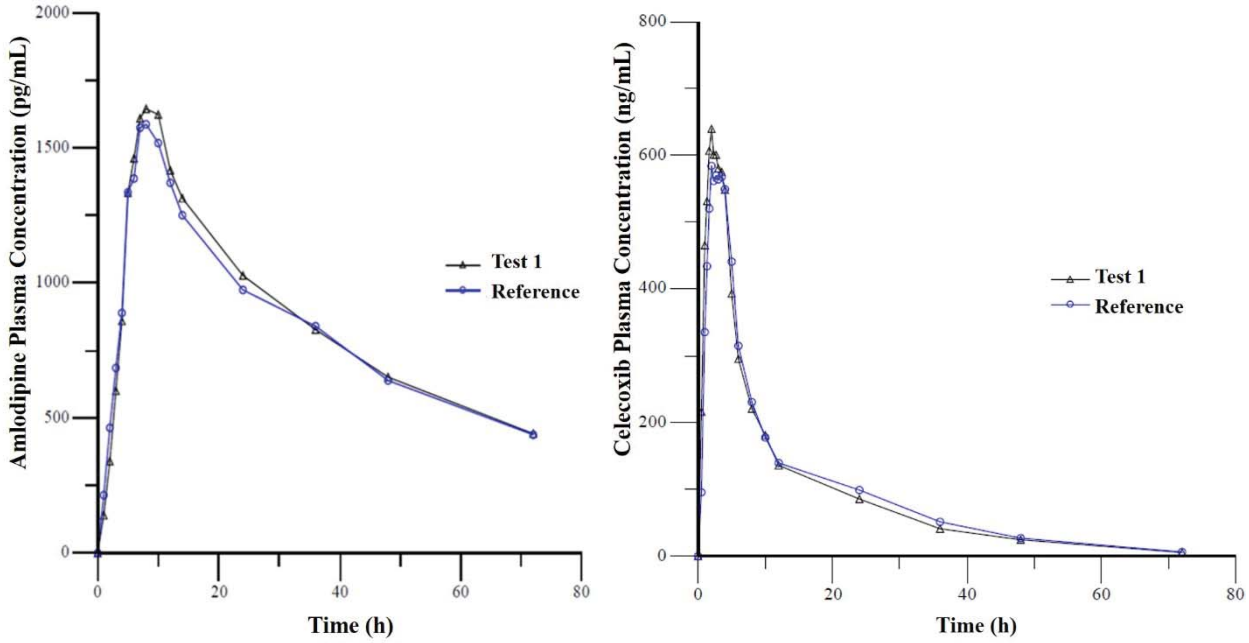


Table 6 shows the pharmacokinetic parameters and GMR (90% CI) of amlodipine and celecoxib following single oral administration of FDC and free combination of amlodipine (2.5 mg) and celecoxib (200 mg) under fasting condition

Amlodipine			
Parameter	**FDC [Test 1 (T)] N = 21**	**Free combination [Reference (R)] N = 21**	**Geometric mean ratio [T/R] (90% CI)**
$AUC_{0\text{-}72\ h}$ (pg*h/mL)	59450 (24)	58028 (25)	103 (98-108)
C_{max} (pg/mL)	1699 (25)	1654 (24)	102 (99-106)
t_{max}@ (h)	8.0 (5.0-10.0)	7.0 (5.0-10.0)	-
Celecoxib			
Parameter	**FDC [Test 1 (T)] N = 21**	**Free combination [Reference (R)] N = 21**	**Geometric mean ratio [T/R] (90% CI)**
$AUC_{0\text{-}72\ h}$ (ng*h/mL)	6357 (42)	6487 (44)	98 (93-104)

$AUC_{0\text{-}inf}$ (ng*h/mL)	6539 (43)	6706 (45)	98 (92-103)
C_{max} (ng/mL)	677 (42)	682 (40)	99 (86-115)
t_{max}@ (h)	2.0 (1.0-4.1)	2.0 (1.3-5.0)	-
$t_{1/2}$ # (h)	11.6 (51)	11.5 (34)	-

Values represent geometric mean (% CV); @ indicates median (range); # indicate values in arithmetic mean (%CV)

Food effect:

Figure 7 shows the average plasma concentration-time profile of amlodipine and celecoxib following single oral administration of FDC of amlodipine (2.5 mg) and celecoxib (200 mg) in healthy subjects under fasting and fed condition.

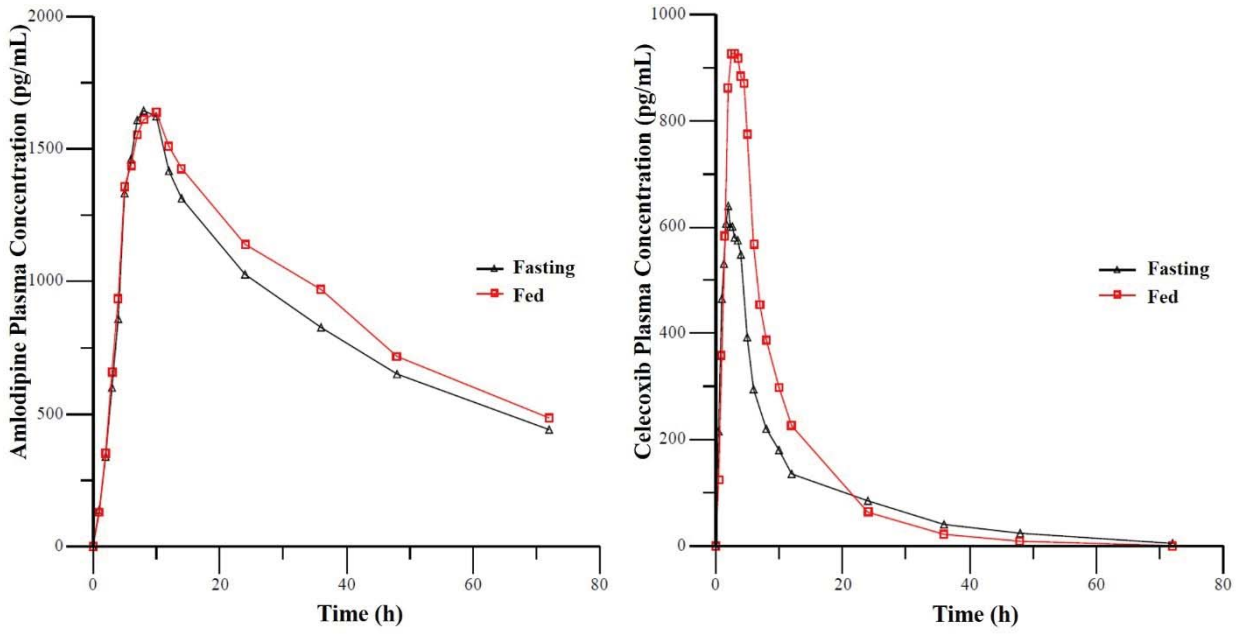


Table 7 shows the pharmacokinetic parameters and GMR (90% CI) of amlodipine and celecoxib following single oral administration of amlodipine (2.5 mg) and celecoxib (200 mg) FDC tablet in healthy subjects under fasting and fed condition.

Amlodipine			
Parameter	**FDC (Test 1) [Fasting] N = 21**	**FDC (Test 3) [Fed] N = 21**	**Geometric mean ratio [Fasting/Fed] (90% CI)**
$AUC_{0\text{-}72\ h}$ (pg*h/mL)	59450 (24)	64879 (25)	109 (105-113)
C_{max} (pg/mL)	1699 (25)	1697 (27)	100 (95-105)
t_{max}@ (h)	8.0 (5.0-10.0)	10.0 (5.0-14.0)	-
Celecoxib			
Parameter	**FDC (Test 1) [Fasting] N = 21**	**FDC (Test 3) [Fed] N = 21**	**Geometric mean ratio [Fasting/Fed] (90% CI)**
$AUC_{0\text{-}72\ h}$ (ng*h/mL)	6357 (42)	8130 (45)	128 (121-135)
$AUC_{0\text{-}inf}$ (ng*h/mL)	6539 (43)	8207 (45)	126 (119-133)
C_{max} (ng/mL)	677 (42)	1261 (36)	186 (161-215)
t_{max}@ (h)	2.0 (1.0-4.1)	3.1 (1.5-10.0)	-
$t_{1/2}$# (h)	11.6 (51)	7.6 (28)	-

Values represent geometric mean (% CV); @ indicates median (range); # indicate values in arithmetic mean (%CV)

D) Study KIT-302-03-01: Clinical pharmacokinetic / pharmacodynamic interaction between amlodipine and celecoxib reference products in patients with newly diagnosed hypertension

The primary objective of this study was to demonstrate a change from baseline to Day 14 in SBP_{day} for amlodipine (10 mg) + celecoxib (200 mg) combination treatment over 14 days is at least 50% of that of amlodipine (10 mg) therapy alone in adults with newly diagnosed hypertension. The secondary objectives were to evaluate the change from baseline in average 24-hour SBP_{24h}, average night-time (01:00 to 06:00) SBP_{night}, average 24-hour diastolic blood pressure (DBP_{24h}), average daytime (9:00 to 21:00) DBP_{day} and average night-time (01:00 to 06:00). In addition, pharmacokinetic drug-drug interaction between amlodipine+celecoxib and amlodipine or celecoxib was also evaluated at Day 14.

This was a multi-center (11 centers), randomized, double blind and placebo controlled study. This study enrolled 152 patients with newly diagnosed hypertension [Age (years): 40-75; resting SBP: ≥135 mmHg and <179 mmHg; SBP_{day}: >135 mmHg at Day 0; Body Mass Index: 18.5-34.9 kg/m^2). Subjects were randomized (1.5:1.5:1:1) to the following treatment arms. For the purpose of blinding, the individual reference drugs were over-encapsulated (OE). Norvasc® (amlodipine besylate tablet, 10 mg) and Celebrex® (celecoxib capsules, 200 mg) were administered once daily (qd) over 14 days in this study.

Arm 1: OE 10 mg amlodipine tablet + OE 200 mg celecoxib capsule

Arm 2: OE 10 mg amlodipine tablet + matched placebo capsule for OE celecoxib capsule

Arm 3: Matched placebo capsule for OE amlodipine tablet + OE 200 mg celecoxib capsule

Arm 4: Matched placebo capsule for OE amlodipine tablet + matched placebo capsule for OE celecoxib capsule

Blood pressure interaction results:

Table 8 shows the baseline, end of study and change from baseline to end of study SBP_{day} (A), SBP_{night} (B), SBP_{24h} (C), DBP_{day} (D), DBP_{night} (E), DBP_{24h} (F) following administration of amlodipine+celecoxib, amlodipine, celecoxib and placebo in patients with newly diagnosed hypertension.

A)

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

B)

Treatment Arm	Mean ± SD SBP_{night} (mmHg) – ITT Population		
	Baseline	End of Study	Change from Baseline to End of Study
Amlodipine + celecoxib (N=49)	126.8 ± 10.5	116.3 ± 9.2	-10.5 ± 10.6
Amlodipine (N=45)	125.73 ± 11.72	119.38 ± 11.86	-6.35 ± 11.35
Celecoxib (N=30)	132.0 ± 16.5	130.3 ± 13.9	-1.7 ± 12.3
Placebo (N=26)	122.5 ± 10.85	121.08 ± 12.37	-1.42 ± 9.15

C)

Treatment Arm	Mean ± SD SBP_{24h} (mmHg) – ITT Population		
	Baseline	End of Study	Change from Baseline to End of Study
Amlodipine + celecoxib (N=49)	141.7 ± 7.0	131.3 ± 8.6	-10.3 ± 8.9
Amlodipine (N=45)	140.65 ± 8.24	132.63 ± 9.41	-8.02 ± 7.6
Celecoxib (N=30)	143.9 ± 8.4	143.4 ± 9.7	-0.5 ± 7.8
Placebo (N=26)	138.8 ± 7.63	137.61 ± 9.28	-1.19 ± 5.87

D)

Treatment Arm	Mean ± SD DBP_{day} (mmHg) – ITT Population		
	Baseline	End of Study	Change from Baseline to End of Study
Amlodipine + celecoxib (N=49)	91.4 ± 8.2	83.9 ± 7.4	-7.5 ± 6.4
Amlodipine (N=45)	88.34 ± 6.92	82.81 ± 7.51	-5.53 ± 5.06
Celecoxib (N=30)	92.5 ± 7.9	90.9 ± 7.4	-1.5 ± 5.6
Placebo (N=26)	91.76 ± 9.1	91.44 ± 10.11	-0.32 ± 5.39

E)

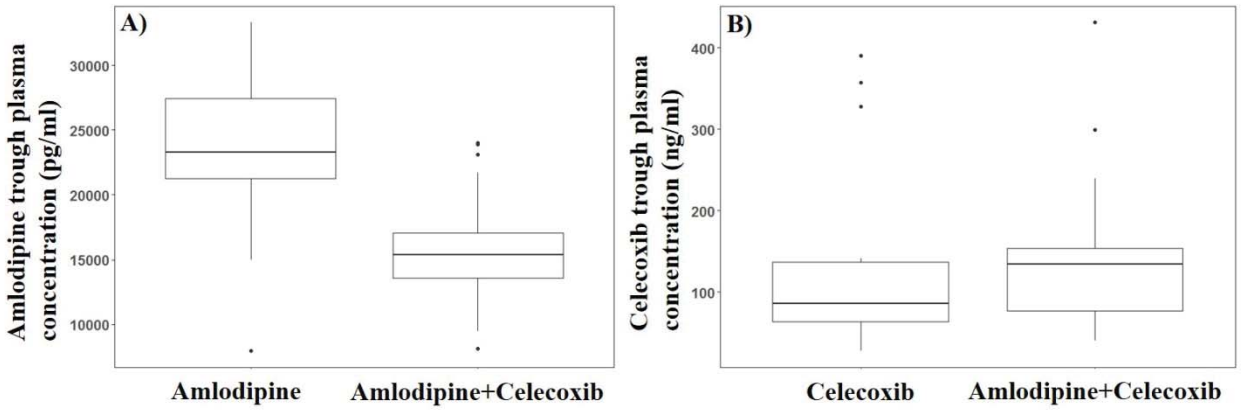
Treatment Arm	Mean ± SD DBP_{night} (mmHg) – ITT Population		
	Baseline	End of Study	Change from Baseline to End of Study
Amlodipine + celecoxib (N=49)	75.8 ± 8.9	68.7 ± 6.7	-7.0 ± 8.6
Amlodipine (N=45)	72.35 ± 8.12	69.11 ± 8.01	-3.23 ± 7.79
Celecoxib (N=30)	76.2 ± 9.5	76.4 ± 8.9	0.3 ± 7.1
Placebo (N=26)	71.52 ± 10.6	71.53 ± 9.24	0.01 ± 6.23

F)

Treatment Arm	Mean ± SD DBP_{24h} (mmHg) – ITT Population		
	Baseline	End of Study	Change from Baseline to End of Study
Amlodipine + celecoxib (N=49)	86.2 ± 7.0	79.1 ± 6.0	-7.1 ± 5.6
Amlodipine (N=45)	83.15 ± 6.07	78.34 ± 7.2	-4.8 ± 4.83
Celecoxib (N=30)	86.5 ± 6.5	86.0 ± 6.5	-0.5 ± 4.6
Placebo (N=26)	84.58 ± 8.42	84.81 ± 8.71	0.22 ± 4.28

Pharmacokinetic interaction results:

Figure 8 shows the plasma trough level of amlodipine (A) and celecoxib (B) following administration of amlodipine+celecoxib and either amlodipine alone or celecoxib alone at Day 14 in patients with newly diagnosed hypertension.



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/s/

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