CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

210045Orig1s000

CLINICAL REVIEW(S)

DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS

Divisional Memo

NDA: 210045 Amlodipine + celecoxib (Consensi) for hypertension and osteoarthritis.

Sponsor: Kitov Pharma

Review date: 27 May 2018

Reviewer: N. Stockbridge, M.D., Ph.D., HFD-110

This memo conveys the Division's decision to approve this application.

This application has been the subject of reviews of CMC (Ladouceur, Sloan, Smith, Jiang, DeCiero, Dave, Li; 27 April 2018), pharmacology/toxicology (Hausner; 15 February 2018), clinical pharmacology (Pillai; 21 May 2018), clinical (McDowell; 23 April 2018), statistics (Kong; 10 April 2018), and pediatrics and maternal health (Mastroyannis; 4 May 2018).

This is a 505(b)(2) application relying upon safety and effectiveness of RLDs for amlodipine and celecoxib. The product will be available as tablets containing amlodipine 2.5, 5, or 10 mg and celecoxib 200 mg. There are no novel excipients. There are no remaining product quality issues, although two PMCs are set for evaluation of elemental impurities and for the dissolution method. The facility inspections were waived. A 24-month expiry is being granted.

There are no new nonclinical studies.

The combination at 10/200 mg was shown to be bioequivalent to the free tablets when administered either fed or fasted.

A multi-center, randomized, parallel, placebo controlled study was conducted to demonstrate that the combination preserved the blood pressure effect of amlodipine; no study was deemed necessary to demonstrate the preservation of pain relief. The study examined the effect on daytime mean systolic pressure, but the 24-hour mean effects were similar. From a baseline SBP of about 148 mmHg, the changes at 14 days were -2.1 on placebo (n=26), -0.5 on celecoxib 200 mg (n=30), -8.8 on amlodipine 10 mg (n=45), and -10.6 mmHg on the combination (n=49), ruling out loss of half of amlodipine's effect. The study was too small to develop meaningful information on subgroups. Adverse events were much as one would expect from the component drugs. There were no study conduct issues, and sites were not inspected. Kitov categorically responded to financial disclosure.

Labeling largely reflects nonclinical information, adverse event data, and special population considerations from the reference monotherapy labels.

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/s/

NORMAN L STOCKBRIDGE
05/29/2018

CLINICAL REVIEW

Application Type	NDA
Application Number(s)	210045
Priority or Standard	Standard
Submit Date(s)	7/31/2017
Received Date(s)	7/31/2017
PDUFA Goal Date	5/31/2018
Division/Office	Cardiovascular and Renal Products/ODE-I
Reviewer Name(s)	Tzu-Yun McDowell
Review Completion Date	4/23/2018
Established/Proper Name	Amlodipine and celecoxib
(Proposed) Trade Name	Consensi®
Applicant	Kitov Pharmaceuticals, Ltd
Dosage Form(s)	Tablets (amlodipine/celecoxib): 2.5mg/200mg, 5mg/200mg and 10mg/200mg
Applicant Proposed Dosing Regimen(s)	Adult recommended starting dose (amlodipine/celecoxib): 5mg/200mg orally qd with maximum dose 10mg/200mg qd. Small, fragile, or elderly patients, or patients with hepatic insufficiency may be started on 2.5 mg/200mg
Applicant Proposed Indication(s)/Population(s)	Patients who require (b) (4) treatment (b) (4) of osteoarthritis and who also require the treatment of hypertension, to lower blood pressure. Lowering blood pressure reduces the risk of fatal and nonfatal CV events primarily strokes and myocardial infarctions.
Recommendation on Regulatory Action	Approve
Recommended Indication(s)/Population(s) (if applicable)	Patients for whom treatment with both celecoxib for osteoarthritis and amlodipine for hypertension are appropriate

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Glossary

AAC	Arthritis Advisory Committee
ABPM	ambulatory blood pressure monitoring
AC	advisory committee
ACE	angiotensin converting enzyme
ADR	adverse drug reaction
AE	adverse event
APAP	acetaminophen
AR	adverse reaction
ARB	angiotensin receptor blockers
BA	bioavailability
BE	bioequivalent
BP	blood pressure
BUN	blood urea nitrogen
CA	calcium
CMC	chemistry, manufacturing, and controls
CRF	case report form
CSR	clinical study report
CV	cardiovascular
DAAAP	Division of Anesthesia Analgesia and Addiction Products
DBP	diastolic blood pressure
DBP_{day}	average daytime ambulatory diastolic blood pressure
DBP_{night}	average nighttime ambulatory diastolic blood pressure
DBP_{24h}	average 24-hour ambulatory diastolic blood pressure
$D_{Sa}RM$	Drug Safety and Risk Management Advisory Committee
ECG	electrocardiogram
FCDP	Fixed combination drug product
FDA	Food and Drug Administration
FPFV	first patient first visit
GI	gastrointestinal
GPC	Guideline for Good Clinical Practice
ICH	International Conference on Harmonization
ITT	intent to treat
MedDRA	Medical Dictionary for Regulatory Activities
NDA	new drug application
NSAID	Non-steroidal anti-inflammatory drug
OA	osteoarthritis
OE	Over-encapsulated

OTC	Over the counter
PD	pharmacodynamics
PI	prescribing information or package insert
PK	pharmacokinetics
PP	per protocol
PT	preferred term
RA	rheumatoid arthritis
RLDs	reference listed drugs
SAE	serious adverse event
SAP	statistical analysis plan
SBP	systolic blood pressure
SBP_{day}	average daytime ambulatory systolic blood pressure
SBP_{night}	average nighttime ambulatory systolic blood pressure
SBP_{24h}	average 24-hour ambulatory systolic blood pressure
SOC	systemic organ class
TEAE	treatment emergent adverse event
UK	United Kingdom
US	United States

1. Executive Summary

1.1. Product Introduction

KIT-302 (Consensi®) is a fixed combination drug product (FCDP) consisting of amlodipine besylate, a calcium (Ca) channel blocker antihypertensive drug and celecoxib, a non-steroidal anti-inflammatory drug (NSAID). Both drug components have been marketed in the United States (US) and worldwide for decades as individual branded and generic prescription drug products. KIT-302 is a "convenience reformulation" FCDP developed to improve patient compliance.

The proposed indication for KIT-302 is for patients who require (b) (4) treatment (b) (4) of osteoarthritis (OA) and who also require the treatment of hypertension.

The formulation of KIT-302 is a single immediate release tablet with three dosage forms (amlodipine/celecoxib): 2.5mg/200mg, 5 mg/200mg (recommended starting dose) and 10mg/200mg. KIT-302 is to be taken orally once daily.

1.2. Conclusions on the Substantial Evidence of Effectiveness

KIT-302 was shown to be statistically "non-inferior"[1] to amlodipine on the antihypertensive effect in patients with newly diagnosed hypertension.

1.3. Benefit-Risk Assessment

[1] Non-inferiority was defined for the combination therapy as preserving 50% of the effect of the amlodipine monotherapy

Benefit-Risk Integrated Assessment

KIT-302 (Consensi®) is a "convenience reformulation" fixed combination drug product (FCDP) of amlodipine and celecoxib. The proposed indication is for patients who require (b) (4) treatment (b) (4) of osteoarthritis (OA) and who also require the treatment of hypertension. The combination of amlodipine and celecoxib successfully preserved more than half of antihypertensive effect of amlodipine in patients with newly diagnosed hypertension requiring chronic pharmacological therapy. Demonstration of the clinical safety of KIT-302 primary relies on the referenced listed drugs (RLDs)- Celebrex® (celecoxib) capsules and Norvasc® (amlodipine besylate) tablets. (b) (4) I recommend approval of KIT-302 for (b) (4) patients for whom treatment with both celecoxib for osteoarthritis and amlodipine for hypertension are appropriate.

Amlodipine and celecoxib have been approved and marked in the US and worldwide for decades and the safety profile of both drugs was well established. Celecoxib is one of the NSAIDs indicated to treat OA. According to the applicant, a sizeable amount of OA patients (~50%) used celecoxib chronically (>90 days of therapy). It is estimated that about 12% of OA patients concomitantly take celecoxib and amlodipine. KIT-302 is intended to facilitate once a day dosing for this subset of patients requiring both of the individual components. For a convenience claim, the Agency only requested a single pivotal study using ambulatory blood pressure monitoring (ABPM) to study the effect of celecoxib on the efficacy and safety of amlodipine in patients with hypertension. A pharmacodynamic (PD) interaction study for pain control in OA patients was not required as per the agreement with the Agency. The application was submitted under the 505(b)(2) pathway with 4 bioequivalent (BE) studies and one pivotal study.

In the pivotal study supporting the approval of KIT-302, the blood pressure (BP) reduction effect was observed in both the combination (amlodipine + celecoxib) and amlodipine arms after 14 days of treatment; while there were no substantial changes in BP in the celecoxib and placebo arms. The combination arm was statistically non-inferior to the amlodipine arm on BP reduction. In fact, there was a trend of an enhancement of efficacy for the combination arm with an average of 10.6 mmHg decrease from baseline in average daytime systolic BP (SBP_{day}) compared to 8.8 mmHg decrease in the amlodipine arm. The greater BP reduction in the combination vs. amlodipine arm was observed in other secondary endpoints (i.e. other ABPM parameters) and most obvious during night time with an average difference of about 4 mmHg. This result is unexpected and the mechanism for the observed synergistic BP effect in the combination arm is unclear. The mean plasma amlodipine concentration in the combination arm was found to be about one third lower than that in the amlodipine arm, which is contrary to the observed synergistic BP effect and raises the possibility that these findings are due to chance. Overall, the efficacy results successfully demonstrate that celecoxib does not impair the antihypertensive effect of amlodipine.

The safety of KIT-302 primarily relied on the FDA's previous findings for the RLDs. In the pivotal study, the combination of amlodipine and celecoxib had a similar safety profile compared to that in the amlodipine and celecoxib arms. There were no new safety signals and no safety issues to preclude the approval of KIT-302.

The major review issue for this application is labeling. First, there is conflicting labeling language with regard to cardiovascular (CV) risk in the proposed prescribing information (PI) for KIT-302. At present, all prescription NSAIDs carry a boxed warning for an increased risk of serious adverse CV and thrombotic events; while a claim for beneficial effects on CV outcomes was added in all anti-hypertensive drugs per the 2011 Guidance for Industry-"Hypertension Indication: Drug Labeling for Cardiovascular Outcome Claims". It would be troublesome to keep these inconsistent statements in one PI. Given the labeled CV risk for NSAIDs and the lack of long-term CV outcome study conducted with KIT-302, I recommend to keep the boxed warning and remove the claim about beneficial effects on CV outcomes from the indication. (b) (4) KIT-302 should only be indicated for the subset of OA patients for whom treatment with both celecoxib for osteoarthritis and amlodipine for hypertension are appropriate. Lastly, celecoxib and all NSAIDs are supposed to be used at the lowest dose possible for the shortest time needed due to the concern about CV risk. Therefore, it is expected that patients may temporarily or permanently discontinue KIT-302 for pain management during therapy. This could be problematic with respect to the management of hypertension if patients are not properly informed about the risk of stopping KIT-302. Language regarding an appropriate action to start an alternative antihypertensive treatment when stopping KIT-302 should be included in the PI (b) (4) A risk evaluation and mitigation strategy is not necessary.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• OA is the most common joint disorder in the US. This chronic disease occurs mostly among the elderly and is more prevalent in women than men. • Pain from OA is a key symptom in the decision to seek pharmacologic therapies and a precursor for disability. • Hypertension is a major risk factor for adverse CV events and many serious medical conditions including chronic kidney disease. • Despite a wide variety of therapeutic options, it is estimated that about half of hypertensive population do not have their BP under control to the target level.	OA and hypertension are both important health problems mostly prevalent among the elderly. KIT-302 with the once a day administration of its individual component when used together for the intended population could potentially improve patient compliance.
Current Treatment Options	• Available therapies for OA are limited and consist primarily of acetaminophen, opioids and NSAIDs. • NSAIDs remain important therapeutic options for chronic treatment of OA despite the known gastrointestinal (GI) toxicity and CV risk. • Celecoxib is the only Cox-2 inhibitor (i.e. selective NSAIDs) available in the US. Cox-2 inhibitors are known for lower risk of GI toxicity. • There are various options for antihypertensive treatment (use alone or as an add-on therapy). The primary pharmacologic classes include thiazide or thiazide-type diuretics, angiotensin converting enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARBs), Ca channel blockers.	KIT-302, a "convenience reformulation" FCDP, is intended to be used in a subset of OA patients who require (b) (4) treatment for both pain and hypertension. It is developed to improve patient compliance with the once a day (qd) administration.
Benefit	• The NDA was supported by a single pivotal study- multi-center, randomized, double-blind, placebo controlled study to evaluate the effect of celecoxib on the antihypertensive effect of amlodipine using ABPM. Eligible subjects were randomized 1.5:1.5:1:1 to one of the	The pivotal study demonstrated that the combination of amlodipine and celecoxib successfully retained antihypertensive effect of amlodipine and therefore provided the

<table>
<tr><th>Dimension</th><th>Evidence and Uncertainties</th><th>Conclusions and Reasons</th></tr>
<tr><td></td><td>four treatment arms: combination (amlodipine + celecoxib), amlodipine, celecoxib and placebo. The primary objective was to demonstrate the mean reduction of average daytime systolic blood pressure (SBP_{day}) in the combination arm was no less than half of that in the amlodipine monotherapy arm.
• A total of 152 randomized patients received at least one administration of the study drugs and 150 were in the intent to treat (ITT) population for the primary efficacy analysis. The Pharmacokinetic (PK) drug-drug interactions were evaluated in a subset of subjects (n = 70). The results of the primary efficacy analysis are listed below:
<table><tr><th>Treatment arm</th><th>N</th><th>Baseline Mean (SD)</th><th>End of Study Mean (SD)</th><th>Change from baseline</th></tr><tr><td>Amlodipine + celecoxib</td><td>49</td><td>148.7 (7.4)</td><td>138.1 (9.8)</td><td>-10.6 ± 9.2</td></tr><tr><td>Amlodipine</td><td>45</td><td>147.6 (8.7)</td><td>138.7 (9.6)</td><td>-8.8 ± 8.1</td></tr><tr><td>Celecoxib</td><td>30</td><td>150.6 (9.0)</td><td>150.1 (10.0)</td><td>-0.5 ± 8.8</td></tr><tr><td>Placebo</td><td>26</td><td>147.2 (8.8)</td><td>145.1 (10.1)</td><td>-2.1 ± 8.2</td></tr></table>
The mean estimate of "(BP reduction from the combination arm)– ½ (BP reduction in the amlodipine arm)" was -6.18 with 95% CI of (-9.15, -3.21) which was below zero. FDA statistical reviewer confirmed that these results indicate that the combination therapy retained at least half the effect of amlodipine on $SBP_{day.}$ A more conservative analysis adjusting for the placebo effect also supported the conclusion.
• There was a trend of an enhancement of efficacy observed in the combination arm compared to the amlodipine arm in the pivotal trial.</td><td>evidence supporting the indication of KIT-302 for the treatment of hypertension in OA patients.</td></tr>
</table>

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	The mechanism supporting this observed finding is unclear. The PK finding shows that the mean plasma amlodipine concentration in the combination arm was about one third lower than that in the amlodipine arm. This PK finding did not make much sense given the observed efficacy results. It is possible that the synergistic efficacy results and/or PK finding were due to chance. • Other supportive evidence came from a recent large CV safety trial in which an ABPM substudy indicates a modest BP effect of celecoxib in patients with OA or RA[2].	
Risk	• The clinical safety profile of amlodipine and celecoxib is well established. • In the pivotal study, the safety profile of the combination of amlodipine and celecoxib is similar to that of the amlodipine or celecoxib arm. No new safety signal was identified. • Both amlodipine and celecoxib are known to elevate liver enzymes. The pivotal study is limited in size and treatment duration to assess the long-term effect of amlodipine + celecoxib on liver function. • There is a concern with respect to properly maintaining antihypertensive treatment when a patient discontinues KIT-302 for pain management.	• Safety profile of the combination of amlodipine and celecoxib is consistent with current PI for Celebrex® (celecoxib) capsules and Norvasc® (amlodipine besylate) tablets. No safety issues preclude the approval of KIT-301. • Adverse events related of elevation of ALT and/or AST are expected to occur during the postmarketing setting based on the safety profile of amlodipine and celecoxib. The risk would not be expected to be any higher than in those currently taking both drugs concomitantly.

[2] Ruschitzka F, Borer JS, Krun H et al. Differential blood pressure effects of ibuprofen, naproxen, and celecoxib in patients with arthritis: the PRECISION_ABPM Trial. European Heart Journal, 38(44) p3282-3292.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
		• Patient should be placed on an alternative antihypertensive therapy, such as amlodipine when KIT-302 is discontinued. BP should be monitored if KIT-302 is stopped and replaced with an equal dose of amlodipine.
Risk and Risk Management	• We believe the risk of KIT-302 can be properly managed through labeling	A risk evaluation and mitigation strategy is not necessary.

1.4. Patient Experience Data

Patient experience data was not submitted as part of this application.

2. Therapeutic Context

2.1. Analysis of Condition

Osteoarthritis (OA) is the most common form of arthritis in the United States. It is characterized by pathology that involves the whole joint, including cartilage deteriorations, bone remodeling, osteophyte formation and joint inflammation, among others, leading to symptoms and loss of normal joint function. OA most commonly affects hands, hips and knees[1].

OA typically becomes symptomatic later in life (after age 50) and symptoms worsen over time, which can lead to functional limitations and disability. The most common symptoms of OA are joint pain, stiffness, limited range of motion and swelling. Pain is a key symptom in the decision to seek pharmacologic therapies and a precursor for disability. Majority of OA patients receive both nonpharmacologic (e.g. physical therapy, exercise) and pharmacologic therapies (see available treatment options in section 2.2) [1,2,3]. OA is the leading cause of disability among older adults worldwide and the most common reason for total hip and knee replacement.

Hypertension is another important medical and public health issue. The prevalence of hypertension increases with advancing age. It is estimated that hypertension affects approximately 70% of the population over age 60, the population also at risk for OA. Hypertension is a major risk factor for CV and renal diseases and remains one of the most important preventable contributor to mobility and mortality. Despite the availability of various classes of antihypertensive agents (see section 2.2), many patients do not achieve target BP goal (<140/90 mmHg or 130/80 mmHg per the new 2017 ACC/AHA guideline). Majority of hypertensive individuals cannot have their BP controlled by 1 drug and require two or more antihypertensive agents selected from different drug classes. The 2017 Hypertension Guideline recommends to initiate therapy with 2 first line agents of different classes for adults with stage 2 hypertension (BP ≥ 140/90 mmHg) and a single agent for adults with stage 1 hypertension[4].

The risk of having either condition increases with advancing age, Hence, it is expected that a sizeable of OA patients also receive antihypertensive treatment. According to the applicant, about 50% of OA patients can be expected to also have hypertension and about 12% of OA patients concomitantly taking celecoxib and amlodipine. KIT-302 with the once a day administration of its individual component when used together for the intended population could potentially improve patient compliance.

2.2. Analysis of Current Treatment Options

There is no approved product for the proposed indication-OA patients must take separate drug products to manage chronic pain and hypertension.

For pain management in OA patients, pharmacologic therapies primarily consist of acetaminophen (APAP), opioids and NSAIDs (Table 1). APAP is available over the counter (OTC) while NSAIDs are available both by prescription and OTC purchases. In addition, APAP and NSAIDs are available in combination with opioids by prescription. APAP is usually the first line therapy for the treatment of mild-to moderate symptoms of OA. NSAIDs is only recommended after APAP failure[2,3].

Table 2 provides a list of oral antihypertensive drugs by pharmacologic class. It should be noted that concomitant use of celecoxib with ACE inhibitors, ARBs or beta blocker may diminish the antihypertensive effect of these drugs.

Table 1 Summary of Most Common Chronic Pain Treatment for OA

Pharmacologic Class/Generic Name	Product Name	Important Safety and Tolerability Issues	Other Comments
Non-Opioid Pain Relievers			
Acetaminophen	Tylenol® many other OTC and prescription pain and cold remedies contain APAP.	Over dose and liver injury	The agency requested manufactures to limit the strength of APAP in prescription drug products to no more than 325 mg per tablet, capsule or other dosage unit Does not reduce inflammation, may be less effective than NSAIDs
NSAIDs		Gastrointestinal side effects Increased risk of CV events	Taking antiulcer agents (e.g. PPIs) along with an NSAID is recommended for patients with high GI risk.
Ibuprofen	Advil®, Motrin®		
Naproxen Sodium	Aleve® (OTC), Anaprox®, Naprelan®, Naprosyn®		
Meloxicam	Mobic®		
Celebrex	Celebrex®		
Diclofenac	Cataflam®, Voltaren®, Zipsor®		
Opioid Pain Relievers*			
Oxycodone	Combined with APAP-Percocet® Combined with ibuprofen-Combunox®	Misuse, abuse and diversion Respiratory depression Hypotensive effect	
Hydrocodone	Combined with APAP-Lorcet®, Lortab®, Vicodin®,Norco® Combined with ibuprofen-Vicoprofen®		
Tramadol	Combined with APAP-Ultracet®		
hydromorphone	Dilaudid®		

*examples of short-acting opioid and opioid-combination products

Table 2 Approved Oral Antihypertensive Drugs

Pharmacologic Class	Approved drugs
Primary agents	
Thiazide or thiazide-type diuretics	chlorthalidone, hydrochlorothiazide, Indapamide, metolazone
ACE inhibitors	benazepril, captopril, enalapril, fosinopril, lisinopril, moexipril, perindopril, quinapril, Ramipril, trandolapril
ARBs	azilsartan, candesartan, eprosartan, irbesartan, losartan, olmesartan, telmisartan, valsartan
Calcium channel blockers-dihydropyridines	Amlodipine, felodipine, isradipine, nicardipine SR, nifedipine LA, nisoldipine
Calcium channel blockers-nondihydropyridines	Diltiazem SR, diltiazem ER, verapamil IR, verapamil SR, verapamil-delayed onset ER
Secondary agents	
Diuretics-loop	Bumetanide, furosemide, torsemide,
Diuretics-potassium sparing	Amiloride, triamterene
Diuretics-aldosterone antagonists	Eplerenone, spironolactone
Beta blockers-cardioselective	Atenolol, betaxolol, bisoprolol, metoprolol tartrate, metoprolol succinate
Beta blockers-cardioselective and vasdilatory	nebivolol
Beta blockers- noncardioselective	Nadolol, propranolol IR, propranolol LA
Beta blockers-intrinsic sympathomimetic activity	Acebutolol, carteolol, penbutolol, pindolol
Beta blockers-combined alpha-and beta-receptor	Carvedilol, carvedilol phosphate, labetalol
Direct renin inhibitor	aliskiren
Alpha-1 blockers	Doxazosin, prazosin, terazosin
Central alpha-agonist and other centrally acting drugs	Clonidine oral, clonidine patch, methyldopa, guanfacine
Direct vasodilators	Hydralazine, minoxidil

Source: 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline 2017[4]

3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

I summarized the important regulatory actions and marketing history for the two RLDs: NDA 020998 for Celebrex® (celecoxib) capsules and NDA 019787 for Norvasc® (amlodipine besylate) in this section.

NDA 020998 for Celebrex® (celecoxib) capsules

Celecoxib was first approved in 1998 for the relief of the signs and symptoms of OA and for relief of the signs and symptoms of rheumatoid arthritis (RA). Celecoxib was subsequently approved for other indications including management of acute pain in adults and treatment of primary dysmenorrhea in 2001, relief of signs and symptoms of ankylosing spondylitis in 2005 and juvenile rheumatoid arthritis in patients 2 years and older in 2006.

The major post-marketing regulatory actions are related to the class effect of NSAIDs on the risk of CV and thrombotic events. The potential increased risk of serious adverse CV and thrombotic events, was first added in the Boxed Warning and Warnings and Precautions sections for prescription NSAIDs labeling in 2005 as a result of a joint Advisory Committee (AC) meeting of the Arthritis Advisory Committee (AAC) and Drug Safety and Risk Management Advisory Committee (D_{Sa}RM) AC held in February 2005. The boxed warning also includes the well described NSAID class risk of serious, and often life-threatening, GI bleeding. A contraindication for use in patient immediately post-operative from coronary artery bypass grafting surgery was also added in all prescription NSAID labeling. The FDA Memorandum in April 2005 recommended to request a written commitment from the sponsor to conduct an additional long-term study (or studies) to address the safety of celecoxib (selective- COX2) compared to naproxen and other appropriate active controls (e.g., other non-selective NSAIDs, appropriate non-NSAID active comparators).

In response to the 2005 AC meeting and the subsequent FDA Memorandum, the *Prospective Randomized Evaluation of Celecoxib Integrated Safety vs. Ibuprofen or Naproxen* (PRECISION) study was launched in 2006 to examine the CV and non-CV safety of celecoxib and non-selective NSAIDS using direct comparisons. The study was led by the Cleveland Clinic and sponsored by Pfizer Inc.

Since the major regulatory actions in 2005, a substantial amount of data from observational and clinical studies has been published on various aspects of the relationship between NSAID use and CV thrombotic risk. A TSI (#1230) was opened in 2011 and a joint AC meeting of the

ACC and D_{Sa}RM was held on February 10-11 2014[3] to discuss data published in 2006 or later that were relevant to further understanding the relationship between NSAIDs and CV risk currently described in NSAID class labeling. The PRECISION trial (on going at the time of the meeting) was also a topic of subject and is expected to provide additional safety information once completed. Following the AC meeting in 2014, the FDA issued a safety communication[4], dated July 9, 2015, announcing the decision to strengthen an existing labeling warning that NSAIDs increase the risk of CV and thrombotic events (also see the CDTL Memo for TSI#1230[5]). The prescription NSAID labels including celecoxib was then revised in 2016 to reflect the following information:

- Uncertainty about the relative CV and thrombotic risk across the class: it was previously thought that all NSAIDs may have a similar CV risk; however new evidence makes it less clear that the CV risk is similar for all NSAIDs but the information is not sufficient to determine whether the risk of any particular NSAID is higher or lower than that of any other NSAID.
- The CV and thrombotic risk can occur early in treatment and may increase with duration of use (there is no "risk-free" period)
- The risk appears greater at higher dose
- NSAIDs can increase CV risk in patients with or without known CV disease or risk factors for CV disease
- There is an increased risk in post-MI patients
- There is an increased risk of heart failure with NSAID use

Table 3 provides the updated boxed warning in the current label of Celebrex®, modified in 2016 (see the full prescribing information for Celebrex®).

[3] https://wayback.archive-it.org/7993/20170111202216/http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/ArthritisAdvisoryCommittee/ucm380874.htm
[4] https://www.fda.gov/Drugs/DrugSafety/ucm451800.htm

[5] http://darrts.fda.gov:9602/darrts/ViewDocument?documentId=090140af80399ab8

Table 3 Boxed warning for CELEBREX

CELEBREX® (celecoxib) capsules, for oral use
Initial U.S. Approval: 1998

WARNING: RISK OF SERIOUS CARDIOVASCULAR AND GASTROINTESTINAL EVENTS
See full prescribing information for complete boxed warning.

- **Nonsteroidal anti-inflammatory drugs (NSAIDs) cause an increased risk of serious cardiovascular thrombotic events, including myocardial infarction and stroke, which can be fatal. This risk may occur early in the treatment and may increase with duration of use. (5.1)**
- **CELEBREX is contraindicated in the setting of coronary artery bypass graft (CABG) surgery. (4, 5.1)**

- **NSAIDs cause an increased risk of serious gastrointestinal (GI) adverse events including bleeding, ulceration, and perforation of the stomach or intestines, which can be fatal. These events can occur at any time during use and without warning symptoms. Elderly patients and patients with a prior history of peptic ulcer disease and/or GI bleeding are at greater risk for serious GI events. (5.2)**

An efficacy supplement was submitted to the Division of Anesthesia Analgesia and Addiction Products (DAAAP), dated June 2017, with the results of PRECISION trial (study A3101172) and the proposed Celebrex PI revised based on the study results. The submission is currently under review. An AC meeting is scheduled on April 24-25 2018 to discuss the clinical implications of the PRECISION trial results.

NDA 019787 for Norvasc® (amlodipine besylate) tablets
Amlodipine besylate was first approved in 1992 for the treatment of hypertension. It was then subsequently approved for chronic stable angina, vasospastic angina and angiographically documented coronary artery disease in patients without heart failure or an ejection fraction < 40%. There were no major regulatory actions except several labeling changes including the addition of CV outcome claims for all antihypertensive drugs per the 2011 Guidance for Industry "Hypertension Indication: Drug Labeling for Cardiovascular Outcome Claims" (see the current PI for Norvasc®).

3.2. Summary of Presubmission/Submission Regulatory Activity

Table 4 Summary of important regulatory activities

Source	Advice from Agency
[redacted] (b) (4)	
IR letter/email requests[4] 2/2011-3/2011	Several IRs and email exchanges took place between FDA and the applicant regarding the design of the clinical study. The main disagreement was whether the clinical study should be conducted in patients with both hypertension and OA.
FDA advice/information request letter[4] 3/18/2011	1. The Division determined that a single, short-term ambulatory BP monitoring study (1-2 week duration) to assess PD interactions between the FCDP in hypertensive patients should be sufficient. 2. For a convenience claim, the agency determined that a PD interaction study for pain control in OA subjects is not required and satisfying BA/BE to RLDs should be sufficient. 3. The Division recommended the applicant to submit a Special Protocol Assessment (SPA) for the planned studies.
FDA SPA Agreement letter for IND 112,830 2/20/2014	Overall, the FDA agreed with the submitted SAP for the pivotal trial (KIT-302-03-01) and provided few comments: <u>Statistics:</u> The statistical reviewers asked the applicant to provide details about their plans on how to combine data from the two phases of the study for efficacy analysis given its adaptive trial design and logistics about their interim trial analyses. <u>Clinical Pharmacology:</u> • The agency recommended to exclude moderate and severe hepatic impaired patients from the pivotal trial. • The agency recommended to collect blood samples for PK assessment in the pivotal study.

[redacted] (b) (4)

Source	Advice from Agency
	• The agency recommended an in vitro assessment to evaluate the impact of over capsulation on the PKs of amlodipine and celecoxib. Clinical: • The Division concurred that the dose levels used in the pivotal study (10 mg amlodipine, 200 mg celecoxib, the two combined and a pure placebo) were acceptable. • The Division advised against using the same BP measurements for determining eligibility and baseline to avoid "regression to the mean effects". • The Division recommended to excluding patients taking calcium channel blockers for other than hypertension indications.
Pre-NDA meeting held on 4/11/2016 Minutes were issued on 5/9/2016	• The Agency advised the applicant to focus their literature search on what will help to explain the paradoxical effects reported in the phase 3 study (i.e. greater BP reduction in the combination arm compared to the amlodipine alone, despite decreased exposure to amlodipine in the combination arm). • The Agency advised the applicant to conduct a BE study on the highest (10 mg amlodipine/200 mg celecoxib) and lowest (2.5/200 mg) doses. • The Agency advised the applicant to combine the relative BA (fasted) and the food effect studies into one single study using a three-way crossover design • The Agency suggested adding labeling language regarding how to properly use this product for pain and antihypertensive management. • The Agency noted that the applicant (b) (4)
Agreed Initial Pediatric Study Plan (ISPS) 5/21/2017	The agency agreed with the agreed iPSP in which a full waiver of pediatric assessment for KIT-302 is requested.

3.3. Foreign Regulatory Actions and Marketing History

KIT-302 is not marketed in other countries. No reported foreign regulatory action.

4. Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

The phase 3 study was conducted at 11 sites in the United Kinden (UK). Majority of sites were small and only two sites had a total number of subjects >25. Efficacy and safety results are generally consistent in these two larger sites. No apparent signal indicates that a particular site drove the overall results of the study. Therefore, the Division concluded that an OSI audit was not requested.

4.2. Product Quality

No issues pertinent to the clinical review

4.3. Clinical Microbiology

No issues pertinent to the clinical review

4.4. Nonclinical Pharmacology/Toxicology

No issues pertinent to the clinical review

4.5. Clinical Pharmacology

There were 4 BE studies submitted to assess bioavailability (BA) and food effect of KIT-302 in heathy volunteers. In addition, PK assessment was performed in a subset of patients in the pivotal study to evaluate the interaction between celecoxib and amlodipine. The BE studies indicate that both high and low strength FDCPs are bioequivalent to RLDs given individually in healthy subjects, both in fasted and fed conditions. Food effect for the FDCP is found to be similar to the RLDs. (See Clinical Pharmacology Review for details). In the pivotal study, assessment of PK drug interaction shows that there were about 30% reduction in amlodipine through concentration for the combination arm (amlodipine +celecoxib) compared to that in the amlodipine arm. This PK finding was not consistent with the primary efficacy results showing that the antihypertensive effects of the combination arm were non-inferior to the

amlodipine monotherapy with a trend towards improvement (see Section 5.2 for the study results).

4.6. Devices and Companion Diagnostic Issues

Not applicable

4.7. Consumer Study Reviews

Not applicable

5. Sources of Clinical Data and Review Strategy

5.1. Table of Clinical Studies

The list of clinical trials relevant to this NDA is located in Table 5. There were 1 pivotal study supporting the approval of KIT-302. The applicant also submitted 4 BE studies to compare BA, safety and tolerability of KIT-302 to RLDs.

Table 5 List of Clinical Studies relevant to this NDA

Trial Identity	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population	No. of Centers and Countries
Controlled Studies to Support Efficacy and Safety							
KIT-302-03-01 (pivotal study)	Randomized, double-blind, placebo controlled ABPM study	Randomized 1.5:1.5:1:1 to Arm1: OE Norvasc® 10 mg amlodipine tablet + OE Celebrex® 200mg celecoxib capsule Arm2: OE Norvasc® 10 mg amlodipine tablet + placebo Arm3: OE Celebrex® 200mg celecoxib capsule+ placebo Arm4: placebo All drugs were taken once a day for 14 days	Change in mean BP from baseline to the final measurement of the study	14 days/a follow-up visit on Day 28	152 Arm1: 49 Arm2: 45 Arm3: 31 Arm4: 27	Adult subjects with newly diagnosed hypertension	11 sites at UK
Other studies pertinent to the review of efficacy or safety (e.g., clinical pharmacological studies)							
(b) (4) -P6-039 (BE)	Randomized, single dose, laboratory-blinded, 2-period, 2-sequence crossover	Test: High strength KIT-302 (200mg celecoxib/10 mg amlodipine tablet) Reference: Celebrex® (200 mg celecoxib capsule) + Norvasc® (10 mg amlodipine tablet); Single dose under fasting condition separated by 21-day	PK parameters	Single dose	40	Healthy adult volunteers	Single center

		washout					
(b) (4)-P6-127 (BE)	Randomized, single dose, laboratory-blinded, 2-period, 2-sequence crossover	Test: High strength KIT-302 (200mg celecoxib/10 mg amlodipine tablet) Reference: Celebrex® (200 mg celecoxib capsule) + Norvasc® (10 mg amlodipine tablet); Single dose under fed condition separated by 21-day washout	PK parameters	Single dose	36	Healthy adult volunteers	Single center
(b) (4)-P7-108 (BE & Food effect)	Randomized, single dose, laboratory-blinded, 3-period, 3-sequence crossover	Test: Low strength KIT-302 (200mg celecoxib/2.5 mg amlodipine tablet) Reference: Celebrex® (200 mg celecoxib capsule) + Norvasc® (2.5 mg amlodipine tablet); Single dose under fasting condition (test and reference) or fed conditions (test only) separated by 21-day washout	PK parameters	Single dose	21	Healthy adult volunteers	Single center
(b) (4) 009/10219	Randomized, single dose, open-label, 3-period, 3 sequence crossover	Test: FCDP Prototype 1 & FCDP Prototype 2 (200mg celecoxib/2.5 mg amlodipine tablet) Reference: Celebrex® (200 mg celecoxib capsule) + Norvasc® (10 mg amlodipine tablet); Single dose under fed condition separated by 14-day washout	PK parameters	Single dose	15	Healthy adult volunteers	Single center

5.2. Review Strategy

Per the agreement with FDA, a single pivotal study (KIT-302-03-01) was conducted in support of this NDA to examine the effect of celecoxib on the efficacy and safety of amlodipine besylate. The efficacy analysis was to evaluate the ambulatory blood pressure results in the ITT population (see section 6). Several sensitivity analyses were performed to confirm the internal validity of the efficacy results in KIT-302-03-01 and to explore the unexpected synergistic antihypertensive effect in patients who received the combination of amlodipine and celecoxib.

Demonstration of the clinical safety of KIT-302 primarily relies on FDA's previous safety findings for the individual RLDs: NDA 02099 (b)(4) for Celebrex® (celecoxib) and NDA 019787 for Norvasc® (amlodipine besylate) tables. The safety data from the phase 3 study, as a supportive safety database, was summarized in section 8.

6. Review of Relevant Individual Trials Used to Support Efficac

KIT-302-03-01: A Prospective Randomized Placebo Controlled Study to Evaluate the Effect of Celecoxib on the Efficacy and Safety of Amlodipine in Subjects with Hypertension Requiring Antihypertensive Therapy

6.1.1. KIT-302-03-01-Study Design

Overview and Objective

- To evaluate the effect of celecoxib on the efficacy and safety of amlodipine in subjects with hypertension
- To evaluate PK drug-drug interactions between amlodipine and celecoxib

Trial Design

This was a multi-center, randomized, double blind, placebo-controlled study. This study was conducted at 11 investigational sites in the UK. Eligible subjects were randomized 1.5: 1.5: 1:1 to one of four treatment arms:

Arm 1 (Combination arm: amlodipine + celecoxib): Over-encapsulated (OE) 10 mg amlodipine tablet + OE 200 mg celecoxib capsule

Arm2 (Amlodipine arm): OE 10 mg amlodipine tablet + matched placebo capsule for OE celecoxib capsule

Arm3 (Celecoxib arm): matched placebo capsule for OE amlodipine + OE 200 mg celecoxib capsule

Arm 4 (Placebo arm): matched placebo capsule for OE amlodipine + matched placebo capsule for OE celecoxib capsule

Following a screening phase, eligible subjects were randomized to one of the 4 arms (Day 0) and a clinical visit was scheduled on Day 1, 6, 7, 13, 14 and 28 (follow-up visit). All drugs were administered orally qd for 14 days. Subjects were instructed to take the study drug in the morning (between 7 and 10 am) at approximately the same time each day with the exception of days when drug was taken to fit the schedule of ABPM measurement (Days 0, 6, and 13 at the time of fitting the ABPM device and Days 1 and 7 when study drug intake was 24 h± 1h later). The first dose was administered in the clinic on Day 0, as were the doses taken on Day 6 and 13. The remainder of the dose were self-administered at home.

This study employed an adaptive design based on the results of the interim analysis to ensure appropriate sample size. Additional subjects were to be enrolled (after initial 150 subjects) and randomized in to either the combination arm or amlodipine arm at a 1:1 ratio.

BP was recorded using ABPM over four 25-hour periods during the trial: Day -1 to Day 0 (baseline ABPM measurement), Day 0 to Day 1, Day 6 to Day 7, and Day 13 to Day 14. The ABPM was collected with the (b) (4) to record measurements every 20 minutes between 9 and 21:59 and every 30 minutes between 22:00 and 8:59. A central laboratory was used for ABPM reading to standardize the results across study sites.

The PK population consisted of a subset of the overall trial population (N = 70 subjects). Blood samples were collected on Day 14 (24 h± 1h post-dose) for the measurement of plasma concentrations of amlodipine and celecoxib. Table 6 shows the schedule event for efficacy, safety and PK assessments.

Table 6 Schedule of efficacy, safety and PK measurements

Event	Screening		Baseline/ 1st Dose	Remainder of Treatment Period					Follow-up
	Initial Screening Visit	Final Screening Visit	Day 0	Day 1	Day 6	Day 7	Day 13	Day 14 (a)	Day 28 (a)
	Day -7 to -2	Day -1							
Informed consent (b)	X								
Record demographic data	X								
Complete medical history	X								
Update of medical history		X	X						
Record prior medications	X	X	X						
Record concomitant medications			X	X	X	X	X	X	X
Height, body weight and BMI	X								
Comprehensive physical examination (c)	X							X	
Targeted physical examination (d)			X	X		X			X
Vital signs (e)	X (e)		X	X		X		X	X
Provide ABPM and instruct on use		X	X		X		X		
25-hour monitoring of BP via ABPM (f)		X	X		X		X		
Orthostatic hypotension evaluation			X	X		X		X	
12-lead ECG	X							X	
Hematology (g)	X							X	
Serum chemistry (g)	X					X (g)		X	
Serum pregnancy test (h)	X								
Urine pregnancy test (h)								X	
Urinalysis (g)	X							X	
Urine drug screen (g)	X								
Review of inclusion/exclusion criteria	X	X	X						
Randomization (i)			X						
Administration of study drug in clinic (j)			X		X		X		
Provide diary to record concomitant medications and study drug details			X						
Review of diary				X	X	X	X	X	X

Source: CSR Table

Inclusion Criteria

- 40 to 75 years of age
- Newly diagnosed hypertension that required treatment
    - Resting SBP≥ 140 mmHg and ≤ 179 mmHg at screening visit
    - SBP_{day} >135 mmHg
- BMI of 18.5 to 34.9 kg/m^2
- No other major medical conditions other than hypertension
- A negative pregnancy test
- Using adequate contraceptive methods while on study

Main Exclusion Criteria (not covered by the inclusion criteria)

- Weight < 55 kg
- Creatinine clearance < 50 ml/min (Cockcroft-Gault equation)
- Fragile health
- Current or recent history of infection
- History of malignancy, MI, stroke, CHF, psychotic disorder, HIV, hepatitis B or C
- Active peptic ulceration or history of GI bleeding
- History of alcoholism and drug use
- Use (within 30 days prior to first of study drugs) of another investigational drug, NSAID, calcium channel blocker, or systemic corticosteroid
- Major surgery within 4 weeks prior to screening
- Known hypersensitivity to amlodipine or celecoxib
- Known CYP2C9 poor metabolizer
- Presence of a malabsorption syndrome (e.g., Crohn's disease or chronic pancreatitis)

Drug Products and Dose Selection

Two commercial formulations were used for this study, Norvasc® (amlodipine besylate) tablets and Celebrex® (celecoxib) capsules.

The dose of amlodipine besylate selected for the study was 10 mg qd. The recommended prescription daily doses in the approved labeling for amlodipine besylate for the treatment of hypertension range from 2.5 mg to 10 mg qd. The recommend initial dose is 5 mg qd.

Reviewer's Comment: The highest amlodipine besylate dose (10 mg) was selected as per FDA's request to increase the statistical power of the study to quantify any PK or PD interaction between amlodipine and celecoxib.

The dose of celecoxib selected for the study was 200 mg qd. The recommended prescription daily doses in the approved labeling for celecoxib for the treatment of osteoarthritis are 200 mg

qd or 100 mg bid. Considering that amlodipine is qd administration and KIT-301 is FCDP, 200 mg qd was selected for celecoxib dose for the trial.

Study Endpoints

Primary Efficacy Endpoint: Mean change in average daytime (9:00-21:00) ambulatory systolic blood pressure (SBP_{day}) from the baseline (Day -1 to Day 0) ABPM measurement to the final (Day 13 to Day 14) ABMP[7] measurement

Secondary Efficacy Endpoints: Average 24-hour ambulatory SBP (SBP_{24h}), average night-time ambulatory SBP (SBP_{night}), average daytime ambulatory diastolic blood pressure (DBP_{day}), average nighttime ambulatory DBP(DBP_{night}) and average 24-hour ambulatory DBP (DBP_{24h}).

Safety was primary evaluated based on reported AEs from the first dose of the study drug to the end of the study.

Statistical Analysis Plan

A serial testing procedure was specified for the primary endpoint. If statistical significance was achieved for the primary comparison, then a secondary comparison was to be performed. If statistical significance was met for both the primary and secondary comparisons, a tertiary efficacy analysis was to be performed.

Primary Comparison:

- To demonstrate the mean reduction in SBP_{day} in the combination arm was no less than half of the mean reduction in SBP_{day} in the amlodipine arm

Secondary Comparison:

- A superiority comparison to determine if celecoxib monotherapy raises SBP_{day} significantly vs. placebo.

Tertiary Comparison:

- A superiority comparison between the combination arm and the celecoxib.

Superiority comparison of the difference between treatment arms for secondary endpoints (i.e. other ABPM parameters) were also performed.

[7] Day 6 to Day8 ABPM measurement or Day 0 to Day 1 ABPM measurement was used if a subject did not complete the full 14 days

Protocol Amendments

Protocol for study KIT-302-03-01 was amended 7 times after the first patient first visit (FPFV) occurred under Version 7 of the protocol. Majority of changes were related to inclusion and exclusion criteria. The primary endpoint was changed from SPB_{24h} to SBP_{day} in Version 10; the rationale was reasonable. A summary of important protocol changes made after the Version 7 is provided below:

Version 8 (Dated 2 July 2014)

- Changed exclusion criterion for SBP at screening from SBP > 169 mmHg to SBP >179 mmHg
- Changed the inclusion criterion regarding newly diagnosed hypertension from "requires" chronic pharmacologic therapy to "may" require…

Version 9 (Dated 15 July 2014)

- Changed the inclusion criterion from SBP ">135 mmHg" to SBP "≥ 145 mmHg and ≤ 179 mmHg".
- Added the definition for "resting" BP as "supine for at least 10 minutes with minimal interaction".

Version 10 (Dated 28 July 2014)

- Changed the primary endpoint from SPB_{24h} to SBP_{day} and associated inclusion criterion
- Changed the inclusion criterion from SBP "≥ 145 mmHg and ≤ 179 mmHg" to "≥140 mmHg"

Version 11 (Dated 3 August 2014)

- Clarification for the interim analysis

Version 12 (Dated 12 August 2014)

- Clarified the inclusion criteria regarding hypertension by revising as follows:
  "Newly diagnosed hypertension that requires chronic pharmacological therapy. Specifically, the subject must meet both of the following criteria:
  a. Resting SBP ≥ 140 mmHg and ≤ 179 mmHg at initial screening visit
  b. SBP_{day} >135 mmHg at Baseline visit (Day 0)

Version 13 (Dated 26 February 2015)

- Changed the upper limit of age from 65 to 75 years
- Changed the approximate study period from 5 to 15 months

Version 14 (Dated 17 July 2015)

- Changed the exclusion criterion regarding a positive drug screen.

6.1.2. KIT-302-03-01-Study Results

Compliance with Good Clinical Practices

KIT-302-03-01 was a foreign clinical study conducted under IND 112,830. Independent ethics committees at each study site reviewed the protocol, the informed consent and all written documents provided. According to the applicant, the study was conducted in compliance with the International Conference on Harmonization (ICH) Guideline for Good Clinical Practice (GPC).

Audit certificate was provided in the CSR Appendix 16.1.8. Documents related to the inter-laboratory standardization methods and quality assurance procedures utilized in the KIT-302-03-01 were submitted in Appendix 16.1.10.

Financial Disclosure

The pivotal study (study KIT-302-03-01) was conducted at 11 Investigational sites in the UK; there was one site that did not randomize any subjects in the study. The chief medical officer of Kitov Pharmaceuticals, Ltd. certifies that he has not entered into any financial arrangement with all participants-investigators/subinvestigators/physician/nurses/manager/coordinator/technician listed in the study (statement 1 in the FDA form 3454).

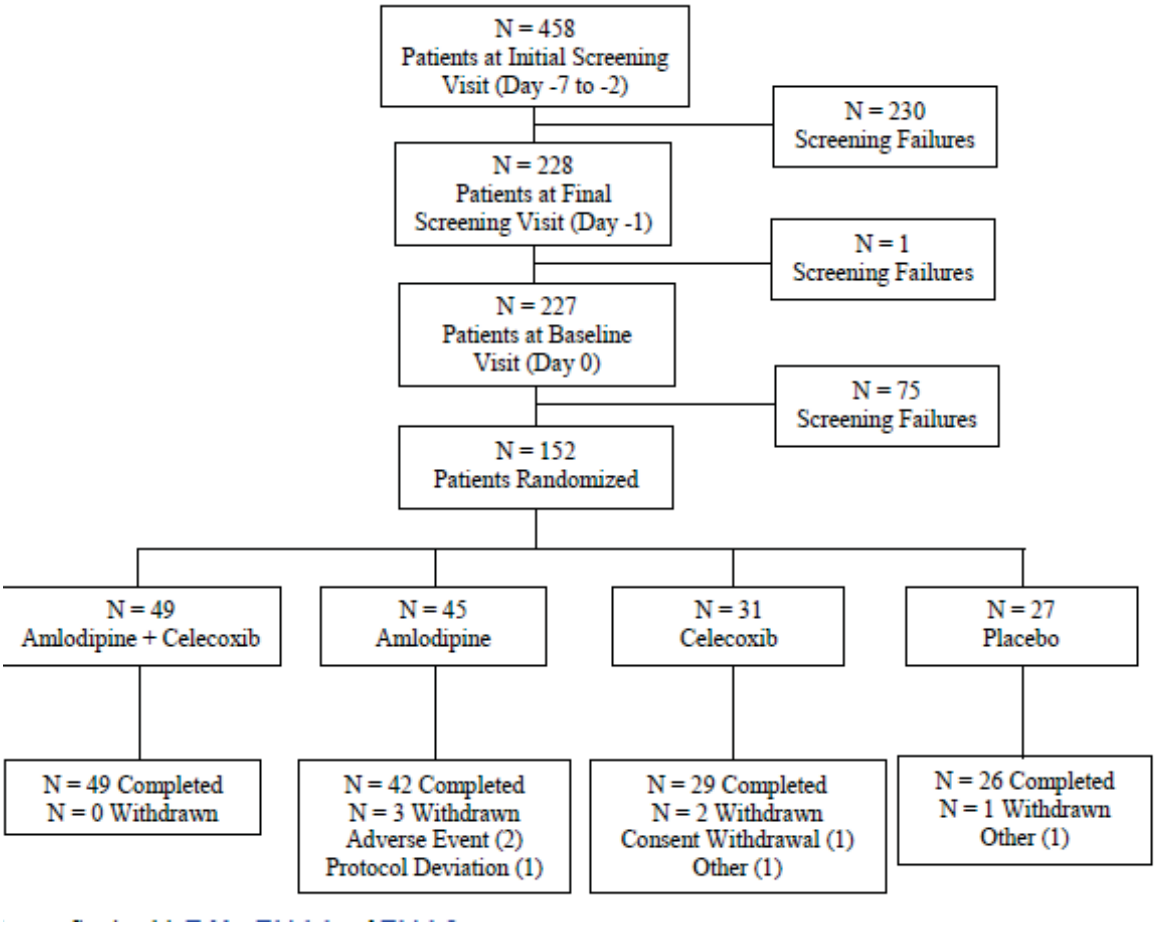
The three formal BE studies were sponsored by (b) (4). The chief medical officer of Kitov Pharmaceuticals, Ltd, as an applicant, certified that all the clinical investigators in the studies did not participate in any financial arrangement with the sponsor (statement 2 in the FDA form 3454).

The nature of these studies minimizes potential bias and there was no evidence to suggest that data integrity was affected by any finance-mediated potential conflict of interest.

Patient Disposition

A total of 458 patients attended the initial screening visit, and of these, 306 (67%) were deemed screening failure at screening visits. Majority of scree failures were due to failure to meet the required definition of hypertension. A total of 152 subjects were then randomized to receive one of four study drugs: 49 in the combination arm, 45 in the amlodipine arm, 31 in the celecoxib arm and 27 in the placebo arm. There were only 6 randomized subjects discontinued from the study; none were from the combination arm (Figure 1). Two subjects in the amlodipine arm discontinued the study due to joint swelling/pain AEs. The ITT population for the primary efficacy analysis consisted of 150 subjects; 1 subject from the celecoxib arm and 1 subject from the placebo arm did not have a valid baseline or post-baseline ABPM measurement; thus was excluded from the ITT population.

Figure 1 Patient Disposition



Source: CSR Figure 1

Protocol Violations/Deviations

There were 12 minor and 11 major protocol violations in the study (a total of 17 patients): 4 in the combination arm, 6 in the amlodipine arm, 4 in the celecoxib arm and 3 in the placebo arm. The most common major protocol violation was “percentage of planned study drug doses completed less than 75% during the study”, which was reported in 3 patients in the amlodipine arm, 2 in the celecoxib arm and 1 in the placebo arm.

These protocol violations were low in numbers, generally balanced and unlikely to affect the efficacy conclusions.

Table of Demographic Characteristics

Demographic and baseline characteristics of the ITT population (N= 150) are shown in Table 7. The median age was 55 years with a range from 40-75 years. Majority of subjects were white (~95%) and male (63%). It is noted that the combination arm and amlodipine arm had more elderly subjects (i.e. ≥65 years). Other demographic and baseline characteristics are in general similar in the four arms.

Table 7 Demographic and baseline characteristics of the ITT population

	Arm1: Celecoxib +Amlodipine (N=49)	Arm2: Amlodipine (N=45)	Arm3: Celecoxib (N-30)	Arm4: Placebo (N=26)
Sex				
Male	32 (65%)	26 (58%)	21 (70%)	16 (62%)
Female	17 (35%)	19 (42%)	9 (30%)	10 (38%)
Age				
Mean years (SD)	57.7 (8.0)	57.3 (9.4)	54.9(8.3)	52.6 (9.2)
Median (years)	56	56	52	52
Min, max (years)	(41,71)	(40,75)	(40,73)	(41,74)
Age Group				
≥ 65 years	12 (25%)	10 (22%)	3 (10%)	3 (12%)
Race				
White	46 (94%)	43 (96%)	28 (94%)	25 (96%)
Black or African American	0 (0%)	2 (4%)	1 (3%)	0 (0%)
Asian	3 (6%)	0 (0%)	1 (3%)	1 (4%)
BMI, mean (SD)	27.8±3.7	29.3±3.7	29.8±3.0	28.5±3.5
Daytime SBP, mmHg (SD)	148±7.4	147.6±8.7	150.8±8.9	147.3±8.6

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

Subjects in this study was relatively healthy except for a recent diagnosis of hypertension. Overall, the frequency and type of previous disease and medication use were similar among the treatment arms.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Compliance was evaluated by counting total number of capsules taken for each subject and calculating percentage of planned dose taken (dividing the total number of capsules taken by 14 days*100). Overall, the compliance was good and similar in the four arms – subjects took on average 97% of planned doses.

About sixty percent of subjects in the study took at least one concomitant medication-51% in the combination arm, 67% in the amlodipine arm, 71% in the celecoxib and 48% in the placebo arm. The most common concomitant medication taken was APAP-contained drug products (~18% of subjects). No apparent imbalance in concomitant medication taken is likely to impact the efficacy results.

Efficacy Results – Primary Endpoint

Table 8 Mean SBP_{day} at Baseline, End of Study and Change from Baseline (ITT population)

Treatment Arm	Mean SBP_{day} (mmHg) – ITT		
	Baseline	End of Study	Difference
Amlodipine + celecoxib (N=49)	148.7±7.4	138.1±9.8	-10.6±9.2
Amlodipine (N=45)	147.6±8.7	138.7±9.6	-8.8±8.1
Celecoxib (N=30)	150.6±9.0	150.1±10.0	-0.5±8.8
Placebo (N=26)	147.2±8.8	145.1±10.1	-2.1±8.2

The primary efficacy comparison was to test for non-inferiority between the amlodipine + celecoxib and amlodipine arms. In the pre-NDA meeting, the agency advised the sponsor to perform the test as follows:

H_0: BP reduction $_{amlodipine + celecoxib}$ - ½ (BP reduction $_{amlodipine}$) = 0 vs. H_A: BP reduction $_{amlodipine + celecoxib}$ - ½ (BP reduction $_{amlodipine}$) <0

The mean estimate of BP reduction $_{amlodipine + celecoxib}$ - ½ (BP reduction $_{amlodipine}$) was -6.18 mmHg with the 95% CI of (-9.15, -3.21), which was below 0 (p<0.0001). Thus, the combination of

amlodipine + celecoxib was statistically no-inferior to amlodipine and successfully retained at least half the effect of amlodipine on SBP reduction. The sensitivity analysis using the per protocol (PP) patient population showed the similar results. The FDA statistical reviewer also estimated the placebo-adjusted effect for the primary comparison. The placebo-adjusted estimate of BP reduction $_{\text{amlodipine + celecoxib}}$ - ½ (BP reduction $_{\text{amlodipine}}$) was -5.13mmHg with 95% CI of (-8.39, -1.87). Thus, the placebo-adjusted treatment effect also supported the conclusion that the combination therapy kept at least half of the effect of the amlodipine monotherapy.

As the primary efficacy comparison was statistically significant, the secondary efficacy comparison testing for superiority of the placebo arm over the celecoxib arm was performed. The difference between the arms (SBP_{day} difference of 1.58 mmHg) was not statistically significant thus the hierarchical testing stopped at this stage.

Subgroup analyses for the primary endpoints

The subgroup analyses by age (≤ 65 vs. > 65) and gender show generally consistent results with the overall ITT population (see the Statistical Review).

Efficacy Results – Secondary and other relevant endpoints

There were several secondary endpoints (i.e. other ABPM measures) and comparisons (i.e. pairwise comparison for each endpoint) in the study. Overall, the results of secondary endpoints were consistent with the pattern observed for the primary endpoints. I summarized the results of secondary endpoints between the amlodipine + celecoxib and amlodipine arms in Table 9 .

Table 9 Mean BP for at Baseline, End of Study and Change from Baseline (ITT population)

ABPM parameters	Mean BP Change from Baseline (mmHg)		
	Amlodipine + celecoxib (N=49)	Amlodipine (N=45)	Difference*
SBP_{day} (Primary endpoint)	-10.6 ± 9.2	-8.8 ± 8.1	-1.8 (-5.4, 1.8)
SBP_{night}	-10.5 ± 10.6	-6.4 ± 11.4	-4.2 (-8.7, 0.3)
SBP_{24h}	-10.3 ± 8.3	-8.0 ± 7.6	-2.3 (-5.7, 1.1)
DBP_{day}	-7.5 ± 6.4	-5.5 ± 5.1	-2.0 (-4.4, 0.4)
DBP_{night}	-7.0 ± 8.6	-3.2 ± 7.8	-3.8 (-7.2, -0.4)
DBP_{24h}	-7.1 ± 5.6	-4.8 ± 4.8	-2.3 (-4.5, -0.1)

* Amlodipine as the reference group

Reviewer's Comment: These results demonstrated the internal consistency of BP lowering effect in the combination arm relative to the amlodipine monotherapy. Although the mechanism for the observed synergistic effect is not clear and could be potentially due to a chance finding, the overall efficacy results support that celecoxib dose not impair the effect of amlodipine on BP reduction. Of note, a modest BP effect of celecoxib in patients with OA or RA has been recently demonstrated in a large CV safety trial[5].

Dose/Dose Response

The pivotal study only investigated the maximum recommended doses of amlodipine (10 mg) and celecoxib (200 mg). KIT-302 is developed with a fixed dose of celecoxib (200 mg) and three dosage forms of amlodipine (2.5 mg, 5 mg, and 10 mg). Dose Response for KIT-302 is relied on previous findings for amlodipine.

Durability of Response/ Persistence of Effect

The treatment effect was examined on Day 14. The durability of response and persistence of effect were not formally tested and relied on FDA's previous findings on the RLDs.

7. Integrated Review of Effectiveness

Not applicable. There was only one pivotal trial for this application.

8. Review of Safety

8.1. Safety Review Approach

The safety of KIT-302 is primarily based on FDA's previous findings on RLDs. The pivotal study serves as a supportive safety database and provides limited additional information due to the size and duration of the study. I only reported the main safety findings from the pivotal study.

8.2. Review of the Safety Database

8.2.1. Overall Exposure

All 152 randomized subjects were to take the study drug orally qd for 14 days. The majority of patients took 100% of the planned study drug dose, including 48 patients (98%) in the amlodipine +celecoxib arm, 42 patients (93%) in the amlodipine arm, 29 patients (94%) in the celecoxib arm and 25 patients (93%) in the placebo arm. Few patients from each arm took drugs less than 75% of the planned dose: 0 patient in the amlodipine + celecoxib, 3 patients in the amlodipine arm, 2 in the celecoxib arm and 1 in the placebo arm. Overall, the exposure was similar in the four arms.

Reviewer's comment: Missing more than 25% of planned doses of stud drugs was considered as a major protocol violation and a basis for excluding a patient from PP analysis. Efficacy results in PP population were consistent with that in the ITT. Overall, no apparent exposure-related issues could impact safety and efficacy results.

8.2.2. Relevant characteristics of the safety population:

See section 6.1.2 for demographic and other baseline characteristics of study population.

8.2.3. Adequacy of the safety database:

The safety of KIT-302 is primarily based on FDA's previous findings on RLDs. The safety database from the pivotal study only serves as a supportive database.

8.3. Adequacy of Applicant's Clinical Safety Assessments

8.3.1. Issues Regarding Data Integrity and Submission Quality

There are no identified issues regarding data integrity. Submission quality is acceptable.

8.3.2. Categorization of Adverse Events

The applicant categorized AEs by systemic organ class (SOC) and preferred term (PT) using MedDRA version 17.0. Investigators assessed attributability of the event to study drug. Adverse Drug Reactions (ADRs) was all AEs assigned a relationship to study drug of either ADR or suspected ADR. The sponsor evaluated orthostatic hypotension by grouping the PTs of orthostatic hypotension, fall, dizziness, dizziness postural or vertigo.

Reviewer's Comment: The categorization of AEs was acceptable.

8.3.3. Routine Clinical Tests

See Table 6 for the safety assessment by the study period. Briefly, AE was evaluated at every time point from baseline including the follow-up point on Day 28. Laboratory chemistry, hematology and ECG assessment were performed on the initial screening visit and Day 14.

Reviewer's Comment: The safety assessment was acceptable.

8.4. Safety Results

8.4.1. Deaths

There were no deaths during the study period in KIT-302-03-01.

8.4.2. Serious Adverse Events

There were no SAEs during the study period in KIT-302-03-01.

8.4.3. Dropouts and/or Discontinuations Due to Adverse Effects

There were only 2 patients discontinued the study due to AE. Both patients were in the amlodipine arm. One AE was related to pain and swelling in the foot and the other AE included

bilateral capillaritis and bilateral ankle swelling. These AEs were mild to moderate severity and resolved except for the pain that was still presence at the final study visit.

8.4.4. Significant Adverse Events

Orthostatic hypotension was pre-defined and evaluated in the pivotal study. Table 10 shows the results of these AEs. All of these AEs were mild and recovered fully.

Table 10 Summary of Treatment Emergent Orthostatic Hypotension AEs in KIT-301-02

	Amlodipine + Celecoxib N=49	Amlodipine N=45	Celecoxib N=31	Placebo N=27
Orthostatic hypotension related AEs	3 (6%)	2 (4%)	0 (0%)	1 (4%)
Orthostatic hypotension	0 (0%)	2 (4%)	0 (0%)	1 (4%)
Dizziness postural	2 (4%)	0 (0%)	0 (0%)	0 (0%)
Dizziness	2 (4%)	0 (0%)	0 (0%)	0 (0%)

Reviewer's Table, Data source: adsl & ae

Reviewer's comment: The number of the event and size of the study were too small to have meaningful comparisons; however, there was no obvious signal indicating imbalance between the arms.

8.4.5. Treatment Emergent Adverse Events and Adverse Reactions

There was a total of 66 subjects (43%) who experienced at least one treatment emergent AE (TEAE) during the study. The most common AEs were headache and peripheral edema. Overall, the observed AEs were consistent to the safety profile of amlodipine and celecoxib. There was no new safety signal identified.

Table 11 Summary of Common Treatment Emergent Adverse Events and Adverse Drug Reactions in KIT-302-03-01:

Treating Emerging AE/PT	Amlodipine + Celecoxib N=49	Amlodipine N=45	Celecoxib N=31	Placebo N=27
N of patients with any TEAE*	21 (43%)	27 (60%)	11 (36%)	7 (26%)
Headache	3 (6%)	5 (11%)	1 (3%)	2 (7%)
Edema peripheral	4 (8%)	7 (16%)	0 (0%)	0 (0%)
Joint swelling	3 (6%)	3 (7%)	0 (0%)	0 (0%)
Diarrhea	1 (2%)	3(7%)	0 (0%)	0 (0%)
N of patients with any ADRs**	15 (31%)	18 (40%)	4 (13%)	1 (4%)

*This table only listed an AE occurring in at least 3 subjects in any arm
**ADRs are the AEs that the investigators assigned to be related to the study drug or suspected to be related to the study drug

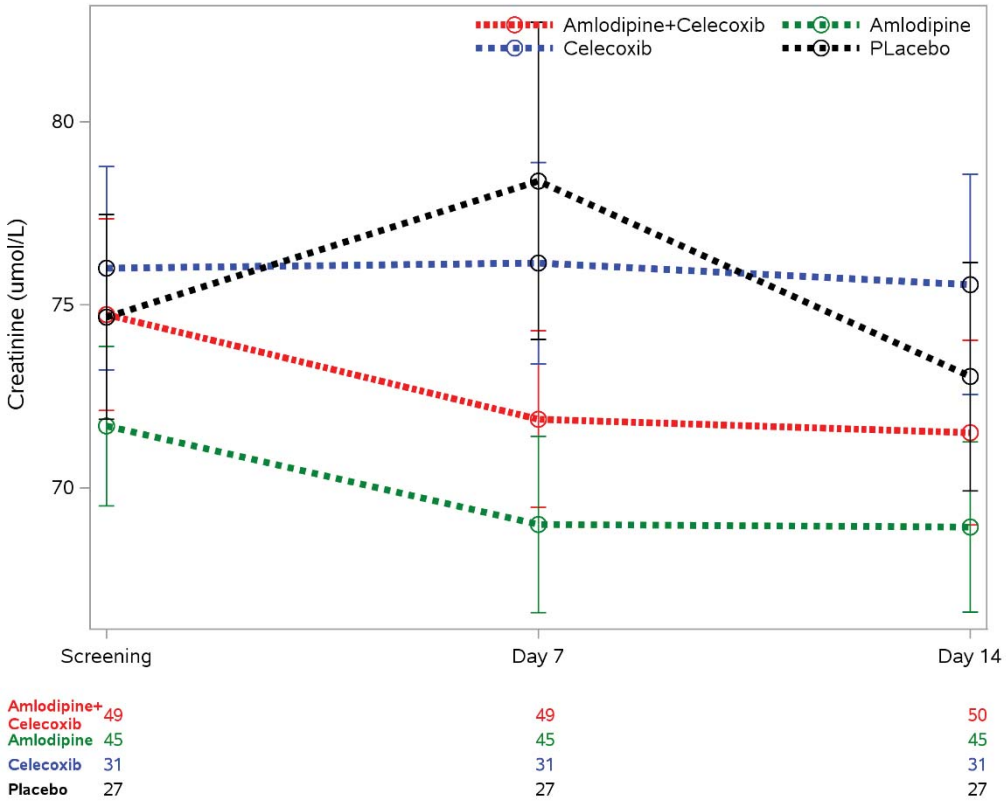
8.4.6. Laboratory Findings

Serum creatinine and electrolytes were measured three times during the study: at screening visit, Day 7 and Day 14; while other laboratory parameters were measured twice at screening visit and Day 14. Overall, there were no meaningful differences among treatment arms for majority of laboratory parameters. Based on the safety profile of celecoxib and amlodipine, I briefly summarized renal-related parameters and liver enzymes in the sections below:

8.4.6.1 Renal-related Parameters:

Creatinine
Serum creatinine decreased from baseline in both combination and amlodipine arms and did not substantially change in the celecoxib and placebo arms. No statistically significant differences were observed among treatment arms.

Figure 2 Time course of serum creatinine in KIT-302-01



Reviewer's Comment: The sponsor mentioned that the observed enhancement in renal function in the combination arm may partially explains the synergistic antihypertensive effect. However, there was no difference between the combination and amlodipine arm in creatinine change. Given the results of blood urea nitrogen (BUN) (see the section below), I think it's unlikely that change of renal function plays a major role for the observed efficacy findings.

Blood Urea Nitrogen (BUN)

The slightly increase in BUN was observed in all treatment arms except the placebo arm (-0.2 mmol/L decrease). The increase in the combination arm met statistical significance (0.66 mmol/L: 95% CI 0.35 to 0.97) and there was a statistical significant difference between the combination and placebo arms. There were 5 subjects (10%) in the combination arm with at least one post-baseline BUN value higher than normal vs. 3 subjects (9.7%) in the celecoxib arm.

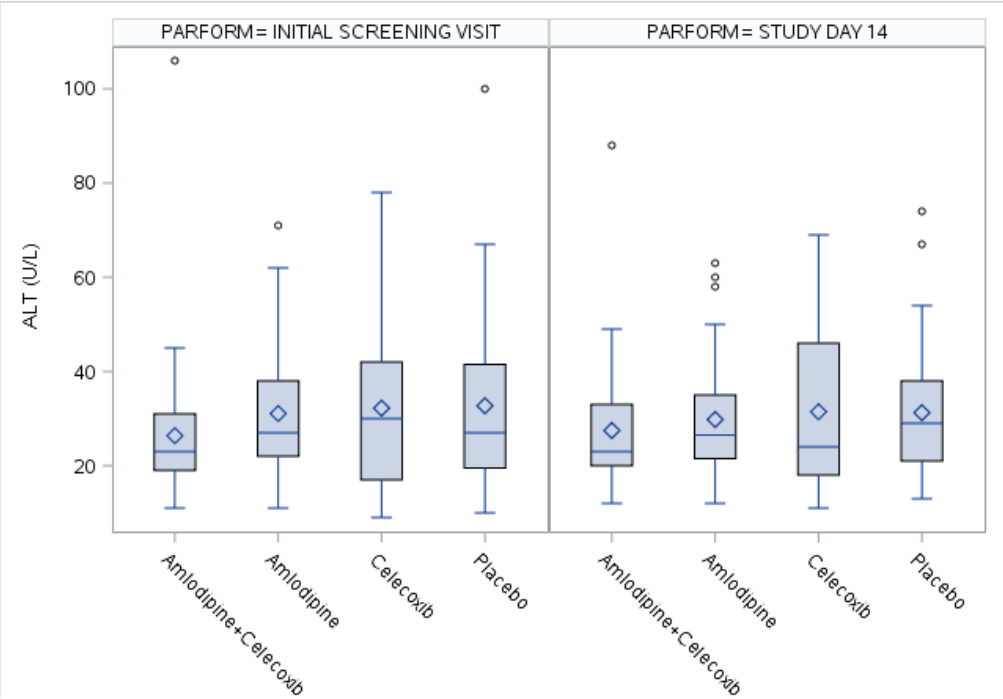
Reviewer's comment: Long term use of celecoxib is associated with renal toxicity while amlodipine may be associated with an improvement of renal function. The results of serum creatinine and BUN from this short duration of the trial did not reveal significant safety concern; though a slightly increase in BUN after 14 day of treatment was observed for the combination arm. The long-term impact of the combination product on renal function is not known.

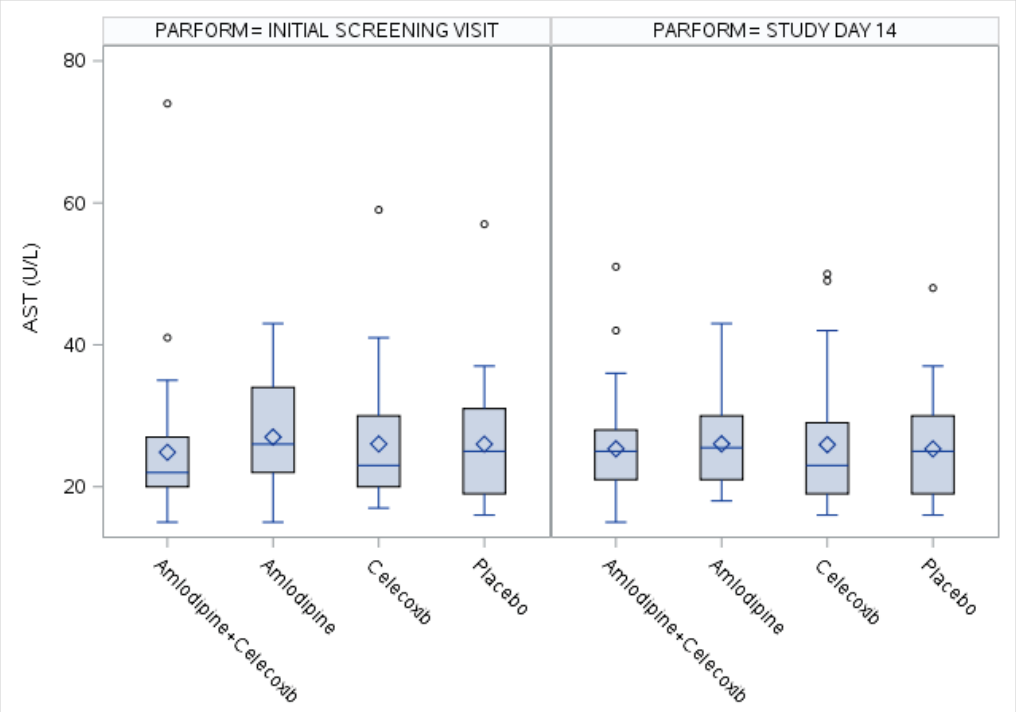
8.4.6.2 Liver Enzymes

Average ALT and AST at baseline and Day 14 were shown in Figure 3. There were minimal changes in liver enzymes in all treatment arms. The outliers in the combination arm at Day 14 were also the outliers at baseline. Very few subjects had abnormal liver enzymes values post treatment and there was no imbalance among treatment arms.

Reviewer's comment: Both celecoxib and amlodipine were known to elevate ALT or AST, thus there is potential that the combination of amlodipine and celecoxib may have synergistic adverse effect on liver enzymes. There was no safety signal from the pivotal study but the long-term effect is not known.

Figure 3 Average ALT and AST at screening visit and Day 14.





8.4.7. Vital Signs

Consistent with the efficacy results, changes in cuff-measured SBP and DBP from baseline on Day 14 was similar between the combination and amlodipine arms. There was no safety signal detected from vital signs.

8.4.8. Electrocardiograms (ECGs)

ECG was assessed at the screening visit and on Day 14. Majority of subjects of each treatment arm had normal ECG findings at both screening and Day 14. No safety signal arose from the ECG findings.

8.4.9. QT

Not applicable

8.4.10. Immunogenicity

Not applicable

8.5. Analysis of Submission-Specific Safety Issues

Not applicable

8.6. Safety Analyses by Demographic Subgroups

The trial is too small to support meaningful subgroup analysis.

8.7. Additional Safety Explorations

Refer to the labeling of each RLD (see Celecoxib® and Norvasc®).for safety issues related to pregnancy, pediatric use and overdose.

8.8. Safety in the Postmarket Setting

8.8.1. Safety Concerns Identified Through Postmarket Experience

Refer to the labeling of each RLD (see Celecoxib® and Norvasc®).

8.8.2. Expectations on Safety in the Postmarket Setting

The clinical safety of celecoxib and amlodipine is well established. Celecoxib and all NSAIDs are supposed to be used at the lowest dose possible for the shortest time needed due to the

concern about the CV risk. One safety concern specific to KIT-302 is the risk of not having continuous antihypertensive treatment when a patient temporally or permanently discontinues KIT-302 for pain management. The risk of stopping KIT-302 and an appropriate action to start an alternative antihypertensive treatment should be adequately informed in the labeling (b) (4)

The pivotal study is limited in size and study duration to assess the long-term effect of amlodipine + celecoxib on renal and liver function. In particular, both celecoxib and amlodipine are known to elevate liver enzymes. Adverse events related of elevation of ALT and/or AST are expected to occur during the postmarketing setting. However, the risk would not be expected to be any higher than in those currently taking both drugs concomitantly.

8.8.3. Additional Safety Issues From Other Disciplines

Not applicable

8.9. Integrated Assessment of Safety

The safety of KIT-302 primary relied on the RLDs. There was no new safety signal identified from the pivotal trial.

9. Advisory Committee Meeting and Other External Consultations

Not applicable

10. Labeling Recommendations

10.1. Specific Safety Studies/Clinical Trials

Not applicable

10.2. Prescription Drug Labeling

We have provided our labeling recommendations (see the edited PI here).

11. Risk Evaluation and Mitigation Strategies (REMS)

There are no safety issues that warrant consideration of a REMS.

12. Postmarketing Requirements and Commitments

Not applicable

13. Appendices

13.1. References

1. Guideline for the Pharmacologic and Non-Pharmacologic Management of Osteoarthritis of the Hand, Hip and Knee. American College of Rheumatology, 2017.
2. Zhang Y and Jordan JM. Epidemiology of Osteoarthritis. Clin Geriatr Med 2010; 26(3):355-369.
3. Chronic Pain Treatment-An Integrated Guide to Physical, Behavioral and Pharmacologic Therapy. American Chronic Pain Association, 2016.
4. Whelton PK, Carey RM, Aronow WS, Casey DE Jr, Collins KJ, Dennison Himmelfarb C, Depalma SM, Gidding S, Jamerson KA, Jones DW, MacLaughlin EJ, Muntner P, Ovbiagele B, Smith SC Jr, Spencer CC, Stafford RS, Taler SJ, Thomas RJ, Williams KA Sr, Williamson JD, Wright JT Jr. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Hypertension. 2017.
5. Ruschitzka F, Borer JS, Krun H et al. Differential blood pressure effects of ibuprofen, naproxen, and celecoxib in patients with arthritis: the PRECISION_ABPM Trial. European Heart Journal, 38(44) p3282-3292.

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/s/

TZU-YUN C MCDOWELL
04/23/2018