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APPLICATION NUMBER:

215727Orig1s000

CLINICAL/STATISTICAL REVIEW(S)

CLINICAL REVIEW

Application Type	505(b)(2)
Application Number(s)	215727
Priority or Standard	Priority
Submit Date(s)	September 19, 2022
Received Date(s)	September 20, 2022
PDUFA Goal Date	March 20, 2023
Division/Office	Division of Cardiovascular and Nephrology (DCN)
Reviewer Name(s)	Adigun, Rosalyn M.D., Pharm.D.
Review Completion Date	February 27, 2023
Established/Proper Name	Colchicine Tablets, USP, 0.5 mg
(Proposed) Trade Name	LODOCO
Applicant	AGEPHA Pharma USA, LLC
Dosage Form(s)	Tablets
Applicant Proposed Dosing Regimen(s)	0.5 mg once daily
Applicant Proposed Indication(s)/Population(s)	To reduce the risk of myocardial infarction (MI), stroke, coronary revascularization, (b) (4) and cardiovascular death among patients with established atherosclerotic disease or with multiple risk factors for cardiovascular disease
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	(b) (4)

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APPEARS THIS WAY ON ORIGINAL

Glossary

ACS	Acute coronary syndrome
AE	adverse event
AF	Atrial Fibrillation
AR	adverse reaction
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CABG	Coronary artery bypass grafting
CAD	Coronary artery disease
CANTOS	Canakinumab Anti-inflammatory Thrombosis Outcome Study
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CHD	Coronary Heart Disease
CI	Confidence interval
COACS	Colchicine for Acute Coronary Syndromes
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
CV	Cardiovascular
CVD	Cardiovascular Diseases
DMC	data monitoring committee
ECG	electrocardiogram
eCTD	electronic common technical document
ETASU	elements to assure safe use
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
FMF	Familial Mediterranean fever
GCP	good clinical practice
GRMP	good review management practice
HMG-CoA	3-hydroxy-3-methylglutaryl coenzyme A
hs-CRP	High-sensitivity C-reactive protein
ICH	International Council for Harmonization

IL	Interleukin
IND	Investigational New Drug Application
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
LDL	Low-density Lipoproteins
LoDoCo	Low-Dose Colchicine
MACE	Major adverse clinical events
MI	Myocardial Infarction
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NME	new molecular entity
NSTE-ACS	Non-ST-elevation acute coronary syndrome
PCI	Percutaneous coronary intervention
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PI	prescribing information or package insert
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PROBE	Prospective, randomized, observer-blinded endpoint
RR	Relative risk reduction
TNFα	Tumor necrosis factor alpha
PSUR	Periodic Safety Update report
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SGE	special government employee
SOC	standard of care
TEAE	treatment emergent adverse event

1. Executive Summary

1.1. Summary of Regulatory Action

Pursuant to §21 CFR 314.126, it is reasonable to conclude that substantial evidence was presented to warrant approval of colchicine (Applicant's product Lodoco™) to reduce the risk of cardiovascular (CV) death, (b) (4) myocardial infarction (MI), (b) (4) stroke, or (b) (4) coronary revascularization (b) (4) (b) (4) in patients (b) (4).

Substantial evidence of effectiveness was based on the single pivotal LoDoCo2 trial[1] with confirmatory evidence from the antecedent LoDoCo trial[2]. Pursuant to §21 CFR 314.54, the Applicant's 505(b)(2) submission relied on the aforementioned publications but without patient-level datasets. The Applicant also relied on FDA's previous finding of safety for the listed drug COLCRYS (colchicine) tablets, 0.6 mg (NDA 022352; Takeda Pharmaceuticals America, Inc). A total of three, non-FDA approved, colchicine formulations were used in the LoDoCo-2 trial (Colgout, Tiofarma colchicine tablets, and Teva colchicine tablets). Colgout was scientifically bridged to COLCRYS and Lodoco (refer to Clinical Pharmacology and CMC review summaries below).

The randomized, double-blind, placebo-controlled LoDoCo-2 trial evaluating patients with stable coronary artery disease (*sample size of 5522 subjects; n= 2762 in the colchicine 0.5 mg daily dosing arm and n= 2760 in the placebo daily dosing arm with a median follow-up duration of 29 months in the colchicine arm and 28.1 months in the placebo arm*), showed a hazard ratio of 0.69 (95% CI 0.57-0.83; p<0.001) for the composite primary efficacy endpoint of CV death, spontaneous MI, ischemic stroke, and UTVR. The components of spontaneous MI and UTVR statistically significantly favored colchicine over placebo. The components of CV death and ischemic stroke trended in favor of colchicine but were not respectively statistically significant. Secondary endpoints were hierarchically ranked but were variable combinations of the components of the primary efficacy endpoint.

There were no data made available for review to evaluate the dependence of treatment effect on body weight. Such data may have addressed the question about whether it was important to match the proposed dose of the Applicant's formulation to the dose used in the LoDoCo trials. Given the proximity of the approved daily dose of the US-FDA approved colchicine product (0.6 mg) to the Applicant's proposed daily dose (0.5 mg) that was used in the LoDoCo trials for the major adverse cardiac event indication, significant pharmacokinetic overlap between the

[1] https://www.nejm.org/doi/full/10.1056/nejmoa2021372
[2] https://pubmed.ncbi.nlm.nih.gov/23265346/

two doses is anticipated, suggesting that either dose would be equally safe and effective. Clinical Pharmacology evaluation (*see clinical pharmacology discipline review below in this docum*ent) specified a low risk for any clinically significant difference in the bioavailability between the Applicant's product and the US-FDA approved product.

The safety data presented in the LoDoCo-2 publication showed a similar distribution and similar number of adverse events between the colchicine arm and the placebo arm (*i.e., non-CV death, cancer, hospitalizations for infection/pneumonia/gastrointestinal disorders, neutropenia, myotoxic effects, myalgia, dysesthesia*).

The benefit in reducing the incidence of CV death, spontaneous MI, ischemic stroke, and UTVR outweighed the risk observed in the intention-to-treat population, thus yielding a recommendation for approval. The recommended labeled indication is (b) (4) (b) (4).

Reviews from clinical pharmacology, pharmacology-toxicology, CMC, labeling, and clinical all endorsed approval of Lodoco. The CDTL evaluation of each discipline's review confirms the endorsement for approval.

1.2. Benefit-Risk Assessment

Table 1. Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Atherosclerotic cardiovascular disease (ASCVD) refers to diseases of the heart and blood vessels caused by the progressive accumulation of atherosclerotic plaques. This process can limit blood flow to the brain (ischemic stroke), heart (coronary artery disease), or obstruct coronary blood flow (acute myocardial infarction). • ASCVD encompasses acute coronary syndromes, stable or unstable angina, coronary artery disease, stroke, transient ischemic attack, or peripheral arterial disease of presumed atherosclerotic origin.[3] • Heart disease and stroke are among the top five leading causes of death in United States and worldwide, accounting for a significant burden of expense on health care services, pharmacotherapy and lost productivity. The direct medical costs from coronary artery disease and stroke are currently estimated to be $126 billion per year and are expected to rise to $309 billion by 2035. [4,5] • Atherosclerosis is a progressive disease characterized by endothelial dysfunction, accumulation of lipids and fibrous elements perpetuating a	Atherosclerotic cardiovascular disease (ASCVD) is a progressive inflammatory disease characterized by the accumulation of plasma lipoproteins and activation of inflammatory pathways in the intima layer of endothelial cells of the affected vessel wall, resulting in luminal obstruction, lesion instability, and rupture or erosion with significant implications and clinical manifestations based on the location of the obstruction and threatened organ.

[3] Amsterdam, Ezra A et al. "2014 AHA/ACC Guideline for the Management of Patients with Non-ST-Elevation Acute Coronary Syndromes: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines." Journal of the American College of Cardiology vol. 64,24 (2014): e139-e228
[4] Murphy SL, Xu J, Kochanek KD, Curtin SC, Arias E. Deaths: Final Data for 2015. Natl Vital Stat Rep. 2017;66(6):1-75
[5] American Heart Association. Cardiovascular Disease: A Costly Burden for America, Projections Through 2035. 2017. www.heart.org/idc/groups/heart-public/@wcm/@adv/documents/downloadable/ucm_491543.pdf.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	chronic inflammatory environment which can remain latent or rapidly progress into an acute event triggered by plaque rupture or thrombosis with partial or total lumen narrowing.[6,7] • There are traditional (older age, sex, family history, hypertension, diabetes, dyslipidemia, obesity, physical inactivity, tobacco use) and nontraditional risk factors (coronary artery calcium (CAC) (apolipoprotein A (ApoA), apolipoprotein B (ApoB), high-sensitivity C-Reactive protein (hsCRP), homocysteine, interleukin 1 (IL1), lipoprotein (a) Lp(a)) associated with ASCVD. Emerging research is focused on targeting nontraditional risk factors associated the residual risk of disease in patients on optimal medical therapy.[8,9]Stable coronary artery disease (CAD) refers to the presence of reversible supply-demand mismatch related to ischemia and precipitated by the presence of atheromatous plaque within the epicardial coronary arteries. • Preclinical models of stable CAD have demonstrated the central role of underlying chronic inflammation in the progression of atherosclerosis independent of statin and anti-platelet therapy. • Disproportionately high rates of adverse outcomes from CAD are caused by acute coronary syndrome and the mechanism of MACE are	

[6] Lusis, A. Atherosclerosis. Nature 407, 233–241 (2000)
[7] Björkegren JLM, Lusis AJ. Atherosclerosis: Recent developments. Cell. 2022;185(10):1630-1645
[8] ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines, Journal of the American College of Cardiology, Volume 63, Issue 25, Part B, 2014, Pages 2889-2934
[9] Grundy S, Stone N, Bailey A, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol. J Am Coll Cardiol. 2019 Jun, 73 (24) e285–e350

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	from plaque disruption with thrombosis or luminal occlusion.[10] • The general approach to evaluation of patients with coronary artery disease involve laboratory assessment biochemical markers of myocardial injury, electrocardiogram, invasive and non-invasive assessment of cardiac anatomy and adequacy of perfusion to myocardium.	
Current Treatment Options	• The current standard of care for patients with stable coronary heart disease include antiplatelet therapy, anti-ischemic therapy, anticoagulation therapy, optimization of blood pressure control, lipid lowering therapy, and diabetes management. • Revascularization with coronary artery bypass grafting (CABG) or percutaneous coronary intervention (PCI) is reserved for patients with refractory symptoms on medical therapy, left main disease, multivessel CAD and ischemic cardiomyopathy with left ventricular systolic dysfunction (LVEF ≤ 50 %).[11],[12] • With treatment strategies targeting optimal lipid management and attenuating the propensity for thrombosis, patients with stable CAD remain at risk for MACE events highlighting unaddressed mechanisms involved in the progression of atherosclerosis.[13] • Inhibition of inflammatory markers (IL-1β) using monoclonal antibodies	Currently available treatment options for patients with stable CAD focuses on risk factor reduction and pharmacotherapy for symptom control and prevention of major complications of myocardial infarction and death. Revascularization with CABG or PCI is recommended in a subset of patients with multivessel disease, left main disease, or systolic dysfunction (LVEF ≤ 50%) when the anatomy is suitable, or in patients with refractory symptoms on medical therapy. However, with these secondary prevention strategies, there remains residual risk for adverse cardiovascular events in patients with CAD.

[10] 2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease
[11] Lawton JS, Tamis-Holland JE, et al. 2021 ACC/AHA/SCAI Guideline for Coronary Artery Revascularization: Executive Summary. J Am Coll Cardiol. 2022;79(2):197-215
[12] Al-Lamee RK, Foley M, Rajkumar CA, Francis DP. Revascularization in stable coronary artery disease. BMJ. 2022;377:e067085. Published 2022 Jun 13. doi:10.1136/bmj-2021-067085
[13] Lusis, A. Atherosclerosis. Nature 407, 233–241 (2000)

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	has been associated with improved clinical outcomes.[14] • Colchicine inhibits the proinflammatory response to cholesterol crystals by reducing macrophage expression of IL-1β, selectins, and inhibits the actions of circulating leukocytes, impairing platelet leukocyte interactions that promote atherothrombosis.[15]	
Benefit	• The effectiveness of colchicine in the treatment of patients with chronic coronary artery disease or risk factors for cardiovascular disease was evaluated in LoDoCo2 trial, a phase 3, randomized, multicenter, double-blind, event driven trial evaluating the efficacy of colchicine compared to placebo, in reducing the incidence of cardiovascular events in patients with chronic coronary disease. • The primary efficacy endpoint was a composite of cardiovascular death, spontaneous (nonprocedural) myocardial infarction, ischemic stroke or ischemia-driven coronary revascularization. • The study met its primary efficacy endpoint. The primary efficacy composite endpoint of cardiovascular death, spontaneous myocardial infarction, ischemic stroke, or ischemia-driven coronary revascularization occurred in 187 patients (6.8%) in the colchicine group and in 264 patients (9.6%) in the placebo group, (HR, 0.69; 95% CI, 0.57 to 0.83; p<0.001)[16] • The effects of colchicine, as compared with placebo, on the primary end point were consistent in the prespecified subgroups defined by demographics, underlying medical conditions, and concomitant medications at baseline.	The results of LoDoCo2 met the pre-specified criteria for success with a statistically significant difference between colchicine and placebo for the primary efficacy endpoint and for the first five secondary efficacy end points within an alpha conserving strategy.

[14] Ridker PM, Everett BM, Thuren T, et al. Antiinflammatory Therapy with Canakinumab for Atherosclerotic Disease. N Engl J Med. 2017;377(12):1119-1131
[15] Deftereos SG, Beerkens FJ, Shah B, et al. Colchicine in Cardiovascular Disease: In-Depth Review. Circulation. 2022;145(1):61-78
[16] Nidorf SM, Fiolet ATL, Mosterd A, et al. Colchicine in Patients with Chronic Coronary Disease. N Engl J Med. 2020;383(19):1838-1847

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• Key secondary composite endpoints of cardiovascular death, spontaneous myocardial infarction, or ischemic stroke occurred in 115 patients (4.2%) in the colchicine group and in 157 patients (5.7%) in the placebo group, (HR, 0.72; 95% CI, 0.57 to 0.92; p = 0.007). • In the prespecified hierarchical testing of the ranked secondary end points within an alpha conserving strategy, the incidence of the first five secondary end points were significantly lower in the colchicine group compared to placebo.	
Risk and Risk Management	• Safety concerns with long-term use of colchicine include the risk of toxicity that can occur with impaired renal function, low body weight (< 70kg), and with co-administration with strong inhibitors of the CYP3A4 and p-glycoprotein efflux pathways. • Certain cardiac medications such as non-dihydropyridine calcium channel blockers (verapamil), or antiarrhythmics (amiodarone) may also alter colchicine clearance. While statins are generally well tolerated with colchicine use, there have been reports of increased risk of myalgias and rhabdomyolysis with combination therapy. • Safety evaluation for colchicine was based on the applicant's reliance on FDA previous findings of safety for the listed product (Colcrys), published literature to support the clinical pharmacology (drug-drug interactions) of the to-be- marketed product, LoDoCo and LoDoCo2 studies supporting the safety of colchicine for long-term use in stable CAD, COPS and Defteros Trial which provide additional data to support the safety of long-term colchicine use at a higher dose exposure. The safety database for colchicine includes approximately 3500 patients in the pivotal, confirmatory, and supportive studies • In LoDoCo trial there were 275 subjects who received at least one dose	No new colchicine associated risks were identified in the studies supporting the use of colchicine in coronary artery disease. Gastrointestinal symptoms were the most commonly reported treatment emergent adverse effect of colchicine therapy resulting in premature discontinuation of therapy. While myalgias were also reported in LoDoCo cohort (1%) and LoDoCo 2 (21.2% in colchicine arm versus 18.5% in placebo) the data in LoDoCo 2 was exclusive to the Netherland cohort as this was not assessed in the Australia cohort. In the Australia COPS trial, no patient in the colchicine arm reported an AE of myalgias compared to 8 patients (2%) in the placebo arm. This risk for colchicine toxicity and drug-drug

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	of colchicine 0.5 mg tablets. • The study provided a median follow-up of 36 months (24 to 44 months). 11% of patients withdrew early (<30 days) for gastrointestinal intolerances and 5% withdrew later (mean period of 2.4 years). The top 2 reasons for withdrawal were due to gastrointestinal intolerance (2.5%) and myalgias (1%). • In LoDoCo 2 trial (N = 2740 received at least one dose of study drug). The median follow-up period was 28.6 months (20.5 to 44.4 months). Adverse events of special interest monitored in the study included myopathy, neuropathy, myositis, and neutropenia which were uncommon in both trial groups. There were no significant imbalances in the rates of malignancy (3.9% versus 3.8%), hospitalization for infection (4.5% versus 5%), pneumonia (1.5 % versus 1.9%), or gastrointestinal symptoms (1.8% versus 1.6%) in the colchicine arm compared to placebo. • In Australian COPS Trial (N = 393 receiving at least one dose of colchicine). The median follow-up period was 28.6 months (20.5 to 44.4 months). Colchicine was administered as 0.5 mg twice daily for the first month, then 0.5 mg daily for 11 months. Dose adjustments were permitted for severe GI symptoms within the first month. By the end of the study, 61 patients (15%) in the colchicine arm had discontinued study medication compared to 33 patients (8%) in the placebo arm. The main reason for premature discontinuation of colchicine were gastrointestinal related (9%) [17]	interactions will be described in the labeling.

[17] Tong DC, Quinn S, Nasis A, et al. Colchicine in Patients With Acute Coronary Syndrome: The Australian COPS Randomized Clinical Trial. Circulation. 2020;142(20):1890-1900

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• In the pilot study of Anti-Inflammatory Treatment With Colchicine in Acute Myocardial Infarction, (N = 77 receiving at least one dose of colchicine), colchicine was administered as a loading dose of 2 mg (1.5 mg initially followed by 0.5 mg 1 hour later) and continuing with 0.5 mg twice daily, or placebo, for 5 days. Dose was adjusted for <60 kg body weight (0.5 mg once daily).[18] 23 of 151 patients discontinued treatment prematurely. 20 patients (26%) in the colchicine arm compared to 3 patients (4%) in the placebo arm. The top reasons for discontinuation were gastrointestinal (diarrhea – 15 versus 1 patient, and nausea/vomiting 3 versus 0) in colchicine compared to placebo.	

Conclusions regarding Benefit-Risk Assessment

Colchicine is a tricyclic alkaloid derived from the flower Colchicum autumnale. It is approved for prevention and treatment of gout flares, and for treatment of familial Mediterranean fever (FMF) in adults and children over 4 years of age. On September 20, 2022, AGEPHA Pharma USA, LLC (Agepha) submitted a 505(b)(2) application relying on the agency's previous findings of safety for the listed product (Colcrys) for the proposed indication "to reduce the risk of myocardial infarction (MI), stroke, coronary revascularization, (b) (4), and cardiovascular death among patients with established atherosclerotic disease or with multiple risk factors for cardiovascular disease".

In support of the proposed indication, the Applicant is relying on two randomized controlled studies from published literature (LoDoCo and LoDoCo2) to demonstrate the efficacy of colchicine for reducing the risk of cardiovascular disease. LoDoCo2 provided substantial evidence of efficacy to support the conclusion that compared to placebo and over the standard of care treatment, colchicine reduced the primary efficacy composite endpoint of cardiovascular death, myocardial infarction, ischemic stroke, or ischemia-driven coronary revascularization in patients with stable coronary artery disease or with risk factors for cardiovascular disease. LoDoCo was a proof-of-concept study and serves as confirmatory evidence for LoDoCo2.

LoDoCo2 randomized 5522 patients with evidence of CAD to colchicine (2762) or placebo (2760) on top of standard care. The composite primary

[18] Deftereos S, Giannopoulos G, Angelidis C, et al. Anti-Inflammatory Treatment With Colchicine in Acute Myocardial Infarction: A Pilot Study. Circulation. 2015;132(15):1395-1403

Dimension	Evidence and Uncertainties	Conclusions and Reasons
endpoint of cardiovascular death, myocardial infarction, ischemic stroke, or ischemia-driven coronary revascularization occurred in 187 patients (6.8%) in the colchicine group and in 264 patients (9.6%) in the placebo group, HR 0.69 (95% CI, 0.57, 0.83) in an intent to treat analysis. The efficacy results were driven by a reduction in non-procedural myocardial infarction and ischemia-driven coronary revascularization. Sensitivity analysis of the primary endpoint in the on-treatment study population was performed in patients who received at least one dose of colchicine or placebo and the treatment effect remained consistent, HR 0.64 (95% CI, 0.53,0.78) providing further evidence of the efficacy of colchicine in the reduction of CV events. The median duration of follow-up was 28.6 months (IQR, 20.5 to 44.4) and the primary endpoint status was available for all but one patient. LoDoCo 2 Trial successfully confirmed the results from the proof-of-concept study LoDoCo trial in a population with stable CAD or at high risk for cardiovascular events. The first key secondary composite end-point event of cardiovascular death, spontaneous myocardial infarction, or ischemic stroke was lower in patients randomized to the colchicine compared to placebo (HR, 0.72; 95% CI, 0.57 to 0.92; p = 0.007). In the prespecified hierarchical testing of the ranked secondary end points within an alpha conserving strategy, the incidence of the first five secondary end points were significantly lower in the colchicine group compared to placebo. This provides further supportive evidence of the effect of colchicine compared to placebo on the primary efficacy endpoint. There were no new safety signals from LoDoCo2 Trial. In conclusion, the benefit/risk assessment of the results from LoDoCo 2 favors the approval of colchicine to reduce the risk of cardiovascular death, myocardial infarction, (b) (4) stroke, (b) (4) coronary revascularization in adults with (b) (4) with risk factors for cardiovascular disease.		

1.3. Patient Experience Data

Table 2. Patient Experience Data Relevant to this Application (check all that apply)

□	The patient experience data that was submitted as part of the application include:	Section where discussed, if applicable
	□ Clinical outcome assessment (COA) data, such as	[e.g., Sec 6.1 Study endpoints]
	□ Patient reported outcome (PRO)	
	□ Observer reported outcome (ObsRO)	
	□ Clinician reported outcome (ClinRO)	
	□ Performance outcome (PerfO)	
	□ Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)	
	□ Patient-focused drug development or other stakeholder meeting summary reports	[e.g., Sec 2.1 Analysis of Condition]
	□ Observational survey studies designed to capture patient experience data	
	□ Natural history studies	
	□ Patient preference studies (e.g., submitted studies or scientific publications)	
	□ Other: (Please specify)	
□	Patient experience data that were not submitted in the application, but were considered in this review:	
	□ Input informed from participation in meetings with patient stakeholders	
	□ Patient-focused drug development or other stakeholder meeting summary reports	[e.g., Current Treatment Options]
	□ Observational survey studies designed to capture patient experience data	
	□ Other: (Please specify)	
√	Patient experience data was not submitted as part of this application.	

2. Therapeutic Context

- Analysis of Condition

Atherosclerotic cardiovascular disease (ASCVD) encompasses acute coronary syndromes, stable or unstable angina, coronary or other arterial revascularization, stroke, transient ischemic attack, or peripheral arterial disease of presumed atherosclerotic origin. ASCVD is the leading cause of morbidity and mortality in the United States and for most racial or ethnic groups worldwide, accounting for a significant burden on health care services, pharmacotherapy and lost productivity.[19,20]

The hallmark of ASCVD is atherosclerosis, the progressive accumulation and transformation of lipoproteins, inflammatory cells, and smooth muscle cells in the intima layer of an affected blood vessel resulting in luminal narrowing which could remain stable, lead to symptoms, or acutely become unstable resulting in an obstruction to blood flow. This process can limit blood flow to the brain (ischemic stroke), heart (coronary artery disease), other organs, or obstruct coronary blood flow (acute myocardial infarction).

Atherosclerosis is a progressive disease of the arteries characterized by endothelial dysfunction from exposure to noxious stimuli, accumulation of lipids and fibrous elements perpetuating a chronic inflammatory environment which can remain latent over time or rapidly progress into an acute event triggered by plaque rupture or thrombosis. Atherosclerotic lesions consist of cellular debris, connective tissue elements, lipids, inflammatory and immune cells resulting in asymmetrical thickening of the intima and luminal narrowing. These plaques can become increasingly complex with the formation of cholesterol crystals (CC) that can trigger an inflammatory response and lead to ulcerations at the luminal surface, hemorrhage from small vessels in the media and activated inflammatory cells in the necrotic core. These events can transform a stable plaque into vulnerable, unstable structure that can rupture, induce thrombosis and obstruct coronary blood flow, eliciting an acute coronary syndrome.[21]

The natural history of plaque progression can follow different trajectories. However, there is often a long and stable subclinical phase, with plaque progression preceding a clinical event. The dynamic process of plaque progression involves alterations of coronary circulation, uncontrolled activation of inflammatory pathways disrupting the endothelium and resulting in atherothrombosis. Patients often present with new-onset chest pain, angina equivalent

[19]Arnett, Donna K et al. "2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines." Circulation vol. 140,11 (2019): e596-e646

[20]Stone, Neil J et al. "2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines." Journal of the American College of Cardiology vol. 63,25 Pt B (2014): 2889-934

[21] Lusis, AJ. Atherosclerosis. Nature. 2000 Sep 14;407(6801):233-41

(dyspnea, arm pain with exertion), symptomatic angina after an established diagnosis, recurrent symptoms after recent or remote revascularization, new onset heart failure, sudden cardiac arrest, or remain asymptomatic with evidence of coronary disease during routine evaluation.[22,23]

Coronary artery disease (CAD) refers to the presence of atheromatous lesions within the epicardial coronary arteries. There are several traditional (advanced age, family history, hypertension, diabetes, hyperlipidemia, obesity, physical inactivity, or tobacco use) and nontraditional risk factors (coronary artery calcium (CAC) (apolipoprotein A (ApoA), apolipoprotein B (ApoB), high-sensitivity C-Reactive protein (hsCRP), homocysteine, interleukin 1 (IL1), lipoprotein (a) Lp(a)) associated with CAD. The current approach to management targets risk factor modification (tobacco cessation, physical activity, weight loss), pharmacotherapy, and revascularization in patients with high-risk features (left main disease), multivessel disease and/systolic dysfunction, and refractory symptoms despite optimal medical therapy. However, despite these interventions, patients with stable CAD remain at risk for major adverse cardiovascular events (MACE) highlighting unaddressed mechanisms involved in the progression of atherosclerosis and highlighting the important role of inflammation in the progression of CV disease. This remains an area of ongoing research to identify targets for new therapies.[24,25,26]

The general approach to evaluation of patients with coronary artery disease involve laboratory assessment biochemical markers of myocardial injury, electrocardiogram, invasive and non-invasive assessment of cardiac anatomy with functional assessment of myocardial perfusion. While cardiac catheterization remains the gold standard for diagnosis of CAD, it is associated with risks and may not always be the appropriate choice. The evolution of non-invasive imaging modalities allows for functional and anatomical information to be obtained with similar diagnostic accuracy and favorable safety profile that the initial choice of testing is contingent on the likelihood of clinically significant disease at the time of initial contact and information gathered is used to inform an appropriate therapeutic strategy.[27]

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[22] Ahmadi, Amir et al. "From Subclinical Atherosclerosis to Plaque Progression and Acute Coronary Events: JACC State-of-the-Art Review." Journal of the American College of Cardiology vol. 74,12 (2019): 1608-1617

[23] Nidorf, Stefan Mark, and Peter Lindsay Thompson. "Why Colchicine Should Be Considered for Secondary Prevention of Atherosclerosis: An Overview." Clinical therapeutics vol. 41,1 (2019): 41-48

[24] Arnett, Donna K et al. "2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease: Executive Summary: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines." Circulation vol. 140,11 (2019): e563-e595

[25] Al-Lamee RK, Foley M, Rajkumar CA, Francis DP. Revascularization in stable coronary artery disease. BMJ. 2022;377:e067085

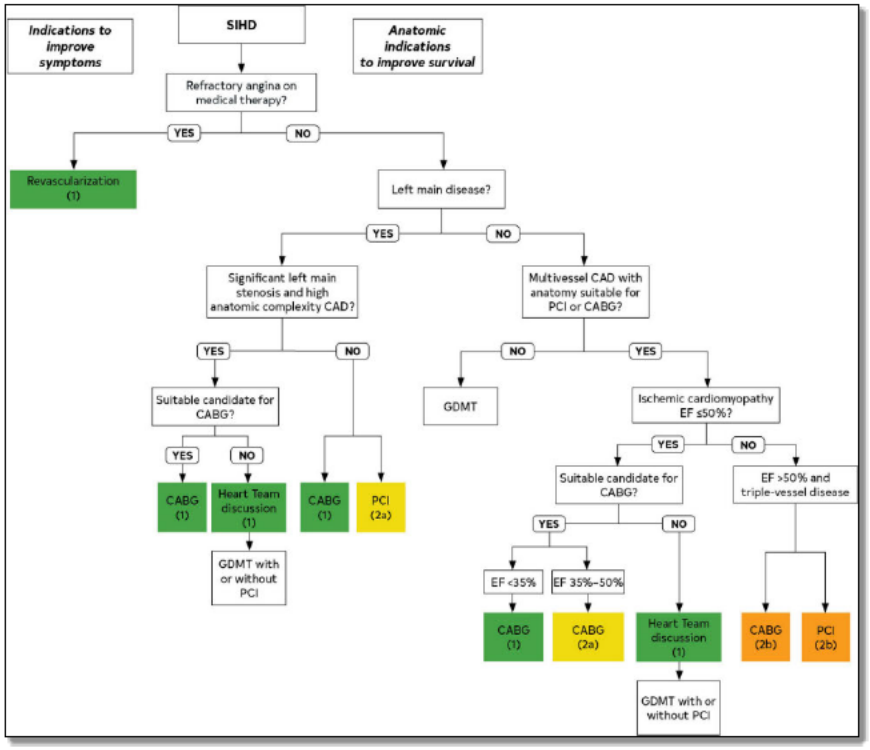
[26] Lawton JS, Tamis-Holland JE, Bangalore S, et al. 2021 ACC/AHA/SCAI Guideline for Coronary Artery Revascularization: Executive Summary: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines [published correction appears in Circulation. 2022; 145(3):e4-e17

[27] Knuuti, Juhani et al. "2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes." European heart journal vol. 41,3 (2020): 407-477

2.2. Analysis of Current Treatment Options

The management paradigm for patients with established coronary artery disease centers on risk factor reduction, optimal pharmacotherapy, revascularization, and management of refractory symptoms to reduce the risk for future adverse cardiovascular events. Revascularization with coronary artery bypass grafting (CABG) or percutaneous coronary intervention (PCI) is reserved for patients with refractory symptoms on medical therapy (Class I recommendation), left main disease or high anatomic complexity CAD (Class I recommendation), multivessel CAD and ischemic cardiomyopathy with left ventricular systolic dysfunction (LVEF < 35 %) (Class I recommendation – CABG) or with LVEF 35% -50% (Class 2a recommendation- CABG).[28,29]

Figure 1: Guideline for Coronary Artery Revascularization



(Source: Lawton JS, et al. Circulation. 2022 ;145(3):e4-e17)

Current recommendations for the treatment of patients with stable coronary heart disease include antiplatelet therapy, anti-ischemic therapy, optimization of blood pressure control, lipid

[28] Al-Lamee RK, Foley M, Rajkumar CA, Francis DP. Revascularization in stable coronary artery disease. BMJ. 2022;377:e067085

[29] Lawton JS, Tamis-Holland JE, Bangalore S, et al. 2021 ACC/AHA/SCAI Guideline for Coronary Artery Revascularization: Executive Summary: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines [published correction appears in Circulation. 2022 ;145(3):e4-e17.

lowering therapy, and diabetes management.[30]

There are several FDA-approved treatments for secondary prevention and current standard recommendations for management of stable CAD have been summarized below.[31]

The 2016 ACC/AHA Guideline Focused Update on Duration of Dual Antiplatelet Therapy in Patients With Coronary Artery Disease, 2012 AHA/ACC Guideline for the Diagnosis and Management of Patients With Stable Ischemic Heart Disease recommendations for management of patients with stable ischemic heart disease include the following:

- Class 1 recommendation for treatment with antiplatelet therapy
- Class 1 recommendation for initiation on anti-ischemic (cardioselective beta-blocker, calcium channel blocker, long-acting nitrates) therapy
- Class 1 recommendation for renin-angiotensin-aldosterone inhibitor therapy
- Class 1 recommendation for Lipid management
- Class 1 recommendation for optimization of blood pressure control
- Class 1 recommendation for coronary revascularization to improve survival in patients with significant disease
- Class IIa recommendation for Diabetes Management

The 2018 AHA/ACC recommendations for management of blood cholesterol in patients with ASCVD include:

- Reduction in low-density lipoprotein cholesterol (LDL-C) with high-intensity statin therapy or maximally tolerated statin therapy to lower LDL-C levels by ≥50%
- In patients with history of multiple major ASCVD events or multiple high-risk conditions, consider adding ezetimibe to maximally tolerated statin therapy when the LDL-C level remains ≥70 mg/dL (≥1.8 mmol/L), or adding a PCSK9 inhibitor if LDL-C level remains ≥70 mg/dL on maximally tolerated statin and ezetimibe therapy

With treatment strategies targeting optimal lipid management and attenuating the propensity for thrombosis, patients with stable CAD remain at risk for MACE events highlighting unaddressed mechanisms in progression of atherosclerosis. Preclinical models of CAD have demonstrated the central role of inflammation in the progression of atherosclerosis

[30] Grundy, Scott M et al. "2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines." Circulation vol. 139,25 (2019): e1082-e1143

[31] Levine GN, Bates ER, Bittl JA, et al. 2016 ACC/AHA Guideline Focused Update on Duration of Dual Antiplatelet Therapy in Patients With Coronary Artery Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines: An Update of the 2011 ACCF/AHA/SCAI Guideline for Percutaneous Coronary Intervention, 2011 ACCF/AHA Guideline for Coronary Artery Bypass Graft Surgery, 2012 ACC/AHA/ACP/AATS/PCNA/SCAI/STS Guideline for the Diagnosis and Management of Patients With Stable Ischemic Heart Disease, 2013 ACCF/AHA Guideline for the Management of ST-Elevation Myocardial Infarction, 2014 AHA/ACC Guideline for the Management of Patients With Non-ST-Elevation Acute Coronary Syndromes, and 2014 ACC/AHA Guideline on Perioperative Cardiovascular Evaluation and Management of Patients Undergoing Noncardiac Surgery [published correction appears in Circulation. 2016 ;134(10):e123-e155

independent of statin therapy and spurred research into the use of anti-inflammatory agents in modifying the progression of atherosclerotic plaques while assessing clinical outcomes in patients with stable CAD. [32]

The association between inflammation and outcomes in CAD from preclinical studies were confirmed in stable CAD patients who demonstrated persistent elevation of inflammatory markers (hsCRP) despite high intensity statin therapy confirming the central role of inflammation in propagation of atherosclerosis. Drug trials evaluating targeted inhibition of inflammatory markers (IL-1β) using monoclonal antibodies validated this concept and was associated with improved clinical outcomes, but further development was halted due to unfavorable benefit-risk profile. Other therapies like methotrexate- a folate antimetabolite known to reduce circulating levels of IL-6, was also studied in stable CAD but did not show a benefit in this population. [33,34]

Colchicine is a tricyclic alkaloid derived from the herbaceous plant Colchicum autumnale. It is approved for prevention and treatment of gout flares, and for treatment of familial Mediterranean fever (FMF) in adults and children 4 years or older.

The mechanism by which colchicine exerts its beneficial effects have not been fully elucidated; however, evidence suggests that colchicine may interfere with the intracellular assembly of the inflammasome complex present in neutrophils and monocytes that mediates activation of interleukin-1β. Additionally, colchicine disrupts cytoskeletal functions through inhibition of β-tubulin polymerization into microtubules and consequently prevents the activation, degranulation and migration of neutrophils thought to mediate some gout symptoms.

The Applicant's evaluation of the effects of colchicine in patients with clinically stable coronary disease is based on two randomized controlled studies LoDoCo and LoDoCo2. The proof-of-concept pilot trial LoDoCo (Low Dose Colchicine) assessed the effects of colchicine 0.5 mg once daily for secondary prevention of cardiovascular disease and LoDoCo2 Trial evaluated the effects of colchicine 0.5 mg daily compared to placebo in patients with stable coronary artery disease on optimal medical therapy.

LoDoCo2 Trial serves as the basis of this submission.

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[32] Ridker PM, Everett BM, Thuren T, et al. Antiinflammatory Therapy with Canakinumab for Atherosclerotic Disease. N Engl J Med. 2017;377(12):1119-1131

[33] Alfaddagh A, Martin SS, Leucker TM, et al. Inflammation and cardiovascular disease: From mechanisms to therapeutics. Am J Prev Cardiol. 2020;4:100130

[34] Ridker PM, Everett BM, Pradhan A, et al. Low-Dose Methotrexate for the Prevention of Atherosclerotic Events. N Engl J Med. 2019;380(8):752-762

3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Colchicine is available worldwide and in the US for over 70 years for the treatment of gout flares and FMF. Colchicine was first approved in the United States in 1961 as a fixed-dose combination drug product (Col-Probenecid) used in treatment of gout. However, since its approval predated the requirement for the demonstration of efficacy, it was reviewed again in 1972 by the National academy of Sciences as part of the Drug Efficacy Study Implementation (DESI) reviews and was deemed effective for the management of chronic gouty arthritis when complicated by frequent, recurrent, acute attacks of gout.

In 2009, the Agency approved single-ingredient oral colchicine product, Colcrys for the treatment of familial Mediterranean fever (FMF) and acute gout flares.

The safety profile for colchicine has been well-documented. Colchicine is generally well-tolerated at normal therapeutic doses with the most common side effects related to gastrointestinal symptoms, e.g., diarrhea, nausea and vomiting. However, therapeutic and toxic levels can result in serious life-threatening adverse events . Oral administration of colchicine generally limits most patients from achieving toxic serum levels since the gastrointestinal adverse effects become rather severe and dose-limiting. Dose adjustments in patients with renal or hepatic impairment and mitigation of drug-drug interactions are important aspects of the safe use for colchicine. Historical references demonstrate cases of fatal colchicine toxicity in patients on standard dosing or when taken with concomitant medications that potentially interact with or are metabolized by similar pathways as colchicine. Medication guides are provided to patients at time of drug dispensing to provide an overview of pertinent safety information.

3.2. Summary of Presubmission/Submission Regulatory Activity

January 8, 2014: Cumulus met with FDA to discuss use of the LoDoCo Trial to support a new NDA. The Agency concluded that the LoDoCo study alone would not provide substantial evidence and a pivotal phase III trial would be needed to support the approval

June 3, 2014: Cumulus submitted a Special Protocol Assessment for the proposed phase III trial, but after review by the Agency, a NO agreement letter was issued in July 2014

November 7, 2017: Cumulus proposed the use of (b) (4) for the purpose of an accelerated approval. After the internal meeting, the sponsor decided not to proceed

September 4, 2019: Cumulus proposes new strategy involving leveraging outcomes from LoDoCo, LoDoCo 2, and COLCUT to support the submission of a NDA
December 2, 2019: Sponsor initiated meeting to discuss leveraging real world data to support LODOCO trial
Pre-NDA meeting with Cumulus to discuss the results of published clinical trial data, mainly study results of LoDoCo-2, and the appropriateness of bridging data for proposed test products and products used in LoDoCo-2 trial.
March 24, 2021: PIND transferred to AGEPHA Pharma Middle East Trading LLC
April 13, 2022: NDA submitted for LODOCO 0.5 mg Tablets under a 505 (b)(2) pathway for a new indication with the 0.5 mg strength
June 11, 2022: Refuse to File letter issued
Sept. 19, 2022: NDA resubmitted
December 7, 2022: Conditional acceptance of proposed proprietary name.
February 28, 2023: Review cycle extended due to a major amendment
April 7, 2023: Change of ownership for NDA to Agepha Pharma FZ LLC

3.3. Foreign Regulatory Actions and Marketing History

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

4.1. Office of Scientific Investigations (OSI)

On November 21, 2022, a Biopharmaceutical Inspections Request was placed. These sites were the locations of the two studies (294-20 and 295-20) which are the pivotal bridging studies supporting the NDA.

The Office of Study Integrity and Surveillance (OSIS) determined that inspections were not needed for the sites listed above based on inspections conducted by the Office of Regulatory Affairs (ORA) for the clinical site in May 2022 which falls within the surveillance interval. OSIS concluded that data from the reviewed studies were reliable.

4.2. Nonclinical Pharmacology/Toxicology

This Pharmacology/Toxicology review focused on the adequacy of the nonclinical bridge that would support labeling regarding nonclinical sections 8.1 and 13.1. Evaluations provided by Biopharmaceutics/OPQ on in vitro dissolution and by CMC/OPQ on quality characterization serve as the basis for the nonclinical bridge.

Nonclinical Discussion of Bridging studies to Support Nonclinical Labeling

Comparative in vitro dissolution study findings

To support the bridge to the RLD (Colcrys) for demonstration of nonclinical safety, the Applicant provided multimedia comparative dissolution between Colcrys (US RLD) and Lodoco (proposed drug product) using purified water, 0.1N HCl, pH 4.5 acetate buffer, and pH 6.8 phosphate buffer. All submitted dissolution profiles demonstrate rapid dissolution (> (b) (4) % in 15 minutes). This dissolution profile and the methods utilized by the Applicant were deemed adequate by the Biopharmaceutics reviewer (details provided in the Biopharmaceutics review in OPQ Integrated Quality Review in DARRTS dated 4/14/23).

CMC characterization

As for the drug product formulation of Lodoco, the CMC review found the formulation contained USP quality colchicine manufactured according to the DMF (b) (4) and was found to be adequate. The excipient levels present in the tablet were adequately justified based on eIID. The 0.5 mg strength tablet is based upon the decades of applicant's experience with the 0.375 mg colchicine tablets" (see OPQ Integrated Quality Review in DARRTS dated 4/14/23).

Based on the OPQ reviewers' assessment of the comparable dissolution profile between Lodoco and the reference drug Colcrys, and the formulation of the drug product as adequate, Pharm/Tox concludes that an adequate scientific bridge to Colcrys has been established to support reliance on Colcrys labeling for nonclinical safety.

4.3. Clinical Pharmacology

This application is primarily relying on the literature reference report for LoDoCo2 study which is a randomized, placebo-controlled, double-blind, safety and efficacy study in patients with chronic coronary disease. Colgout (0.5 mg colchicine tablets) is one of the three products (Colgout, Teva, and Tiofarma formulations) used in the safety and efficacy study LoDoCo2 submitted in this application. The Applicant submitted the results of two PK bridging bioequivalence (BE) studies: (1) 294-20: A fasted state, cross-over study comparing PK of LODOCO (Applicant's colchicine 0.5 mg tablets) and Colgout tablets and (2) 295-20: A fed state, cross-over study comparing PK of LODOCO and Colgout tablets. The Applicant submitted qualitative formulation composition information and multimedia comparative in vitro dissolution data to compare the three immediate release (IR) formulations used in LoDoCo2. In addition, the Applicant submitted multimedia comparative in vitro dissolution data between LODOCO and Colcrys. All dissolution profile comparisons across all pH studied demonstrate rapid and similar dissolution (See Biopharmaceutics review for details).

The Applicant relies on Colcrys for clinical pharmacology information and non-clinical safety information. The application relies on Colcrys for clinical pharmacology information where colchicine is the victim drug in a drug-drug interaction. This is supported by an adequate scientific bridge between the LODOCO and Colcrys based on the following rationale. Colchicine

has PK linearity between the dose range of 0.5 mg to 1.5 mg. The proposed dose of LODOCO (0.5 mg orally once daily) falls within the linear PK range for colchicine, supporting reliance on the clinical pharmacology drug-drug interaction studies with Colcrys where colchicine is a victim drug. Both LODOCO and Colcrys are immediate release (IR) tablets with rapid dissolution. Therefore, there is a low risk for any clinically significant difference in the bioavailability between the two. For Applicant's reliance on non-clinical safety information from Colcrys an adequate scientific bridge is established between LODOCO and Colcrys based on the following rationale. Colcrys is approved for use at daily doses up to 1.8 mg and 2.4 mg for treatment of gout flares and Familial Mediterranean Fever (FMF) respectively. Given the absolute bioavailability of Colcrys is about 45%, the area under the plasma concentration time curve (AUC) for 1.8 mg or 2.4 mg Colcrys is expected to be higher compared to that for LODOCO at the proposed 0.5 mg dose daily dose even if a worst-case scenario of 100% absolute bioavailability is assumed for LODOCO.

The rapid dissolution profiles and the lower proposed strength of LODOCO (0.5 mg) compared to Colcrys reduces the risk of a higher peak plasma concentration (C_{max}) for LODOCO compared to Colcrys. From a clinical pharmacology perspective, the applicant has established an adequate scientific bridge to Colcrys.

5. Sources of Clinical Data and Review Strategy

5.1. Table of Clinical Studies

Table 3. Clinical Trials Submitted in Support of Efficacy and/or Safety

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						
ACTRN12614000093684 (LoDoCo2 Trial)	Randomized, controlled, double-blind trial (phase 3)	Colgout 0.5 mg/ Colchicine 0.5 mg Tiofarma/Teva 0.5 mg tablets once daily versus matching placebo once daily	Components of primary outcome • CV death • Myocardial infarction, • Ischemic stroke • Ischemia-driven coronary revascularization	28.6 (20.5 – 44.4)	552randomized Colchicine-2762 Placebo-2760	Stable CAD	43 centers 2 countries
ACTRN12610000293066 (LoDoCo Trial)	Prospective, randomized, observer-blinded endpoint	Colgout 0.5 mg tablets versus no colchicine	Components of primary outcome • ACS • OHCA • Noncardioembolic stroke	36 (24 – 44)	532 randomized 282 - Colchicine 250 - Placebo	CAD	
	Other studies pertinent to the review of efficacy or safety (e.g., clinical pharmacological studies)						
294-20 (BE)	An open label, balanced, randomized, two-treatment, two-sequence, two-period, cross-over, single-dose, oral bioequivalence study in healthy, adult, human subjects under fasting conditions.	Colchicine 0.5 mg Tablets Oral route administration	Primary Objective: To demonstrate the bioequivalence between Test product (T): Colchicine 0.5 mg Tablets of AGEPHA Pharma with that of Reference product (R): Colgout (Colchicine) 0.5 mg tablets of Aspen Pharmacare Australia Pty	Single dose	Planned -60 Enrolled- 60 Completed-55 Analyzed-60 Withdrawn/drop outs-05 (b) (6)	Normal Healthy Human Subjects	

			Ltd., Australia in healthy, adult, human subjects under fasting conditions. Secondary Objective: To monitor the subject's safety and tolerability of single oral dose of investigational products (IPs).		(b) (6)		
295-20 (BE)	An open label, balanced, randomized, two-treatment, two-sequence, two-period, cross-over, single-dose, oral bioequivalence study in healthy, adult, human subjects under fed conditions	Colchicine 0.5 mg Tablets Oral route administration	Primary Objective: To demonstrate the bioequivalence between Test product (T):Colchicine 0.5 mg Tablets of AGEPHA Pharma with that of Reference product (R):Colgout (Colchicine) 0.5 mg tablets of Aspen Pharmacare Australia Pty Ltd., Australia in healthy, adult, human subjects under fed conditions. Secondary Objective: To monitor the subject's safety and tolerability of single oral dose of investigational products (IPs).	Single Dose	Planned -60 Enrolled- 60 Completed-55 Analyzed-60 Withdrawn/drop outs-05 (b) (6) (b) (6)	Normal Healthy Human Subjects	

5.2. Review Strategy

This is a joint clinical and statistical literature-based review. Clinical reviewer (Rosalyn Adigun, MD, PharmD) and Statistical reviewer (Dali Zhou, PhD) focused on the study design and efficacy results of the pivotal trial (LoDoCo2) submitted in support of the to be marketed drug product LODOCO (Colchicine Tablets, USP, 0.5 mg). The efficacy results from the sponsor will be presented since this is a literature-based review and no data were submitted. Limitations were discussed at the end of the efficacy section. The safety review was performed by Dr Adigun. The applicant has referenced FDA's previous findings of safety for the FDA approved listed drug Colcrys (Colchicine Tablets, USP, 0.6mg) along with supporting published literature to establish the safety of the drug product for the proposed indication.

We have also relied upon the Clinical Pharmacology Review for the analysis of BA/BE studies submitted by the sponsor to establish a bridge between the proposed product (LODOCO) and the formulation used in the LoDoCo2 Trial. We also relied on the Clinical Pharmacology Review for the adequacy of the scientific rationale for the applicant's reliance on the listed drug Colcrys for clinical pharmacology information and clinical safety information.

This review focused on the LoDoCo2 study to evaluate the efficacy and safety of the to be marketed drug product LODOCO (Colchicine Tablets, USP, 0.5 mg) in the intended population.

6. Review of Relevant Individual Trials Used to Support Efficacy

6.1. Design of Clinical Trial - Proof-of-Concept Study

6.1.1. Study Design

Overview and Objective

LoDoCo (Low-Dose Colchicine) Trial was a secondary prevention trial designed to determine whether colchicine 0.5 mg taken once daily can reduce the risk of cardiovascular events in patients with clinically stable coronary disease.

LoDoCo was a prospective, randomized, observer-blinded endpoint trial that randomized 532 patients with stable CAD and on optimal medical therapy with aspirin, clopidogrel, and statins to colchicine 0.5 mg daily or no additional pharmacotherapy. The cohort was followed for a median duration of 36 months (IQR, 24 to 44 months).

Patients randomized to active treatment were given a prescription for colchicine 0.5 mg daily by their referring cardiologist. Adherence and relevant outcome data were obtained at routine clinic follow-up visits, via telephone calls, and at any unplanned hospital admission.

The primary efficacy outcome was the composite of ACS, fatal or nonfatal out-of-hospital cardiac arrest, or noncardioembolic ischemic stroke. Secondary outcomes were individual components of the primary outcome and the components of ACS unrelated to stent disease.

All outcomes were evaluated by an experienced adjudicator blinded to the treatment allocation.

Reviewer's comments: LoDoCo was a small pragmatic trial that enrolled a representative population with CAD. Biological plausibility was established in preclinical models and smaller clinical trials, and clinical experience to establish the safety of colchicine long-term. While the study was controlled, and method of randomization ensures reliability of the study results, the study design predisposes the study to bias (investigator, ascertainment, and reporting) as the treatment allocation was not concealed and knowledge of the treatment arm could influence decision making. The study design could also influence patient adherence patterns. These concerns can influence the interpretability of study results.

6.2. Design of Clinical Trial Intended to Demonstrate Benefit to Patients – LoDoCo2 (Low-dose colchicine for secondary prevention of cardiovascular disease)

6.2.1. Study Design

Overview and Objective

The primary objective of LoDoCo2 trial was to evaluate the clinical efficacy of colchicine 0.5 mg once daily compared to placebo on a background of optimal medical therapy on the incidence of the first occurrence of a composite of CV death, non-procedural myocardial infarction, ischemic stroke, or ischemia-driven coronary revascularization in patients with stable coronary artery disease.

The secondary objectives of the study were to evaluate the efficacy of treatment with colchicine 0.5 mg once daily as compared to placebo in patients with stable coronary artery disease on the incidence of first occurrence of the following pre-specified endpoints ranked in an alpha-conserving strategy.

1. Composite of cardiovascular death, myocardial infarction or ischemic stroke
2. Composite of myocardial infarction or ischemia-driven coronary revascularization
3. Composite of cardiovascular death or myocardial infarction
4. Ischemia-driven coronary revascularization
5. Myocardial infarction

6. Ischemic stroke
7. Death from any cause
8. Cardiovascular Death

Trial Design

LoDoCo2 (Low Dose Colchicine for secondary prevention of cardiovascular disease) was a randomized, multicenter, double-blind, placebo controlled, event driven trial in which 5522 patients with stable coronary artery disease tolerant to colchicine during a 30-day run-in phase were randomized to colchicine 0.5 mg daily or matching placebo on a background of optimal medical therapy.

This trial was designed to confirm the findings of an earlier pilot trial (LoDoCo) - a prospective, randomized, observer-blinded endpoint (PROBE) trial which showed that the risk of acute cardiovascular events was lower among patients with chronic coronary disease who received 0.5 mg of colchicine once daily.

LoDoCo2 was conducted in Australia and in the Netherlands. Recruitment for the study began in 13 centers in Australia (August 2014) but was later expanded to include 30 centers in the Netherlands. The study reached its target enrollment by December 2018, after 5522 subjects had been randomized. The median duration of follow-up was 28.6 months (IQR, 20.5 to 44.4). Details of the enrollment, randomization and follow-up is shown in Fig.1

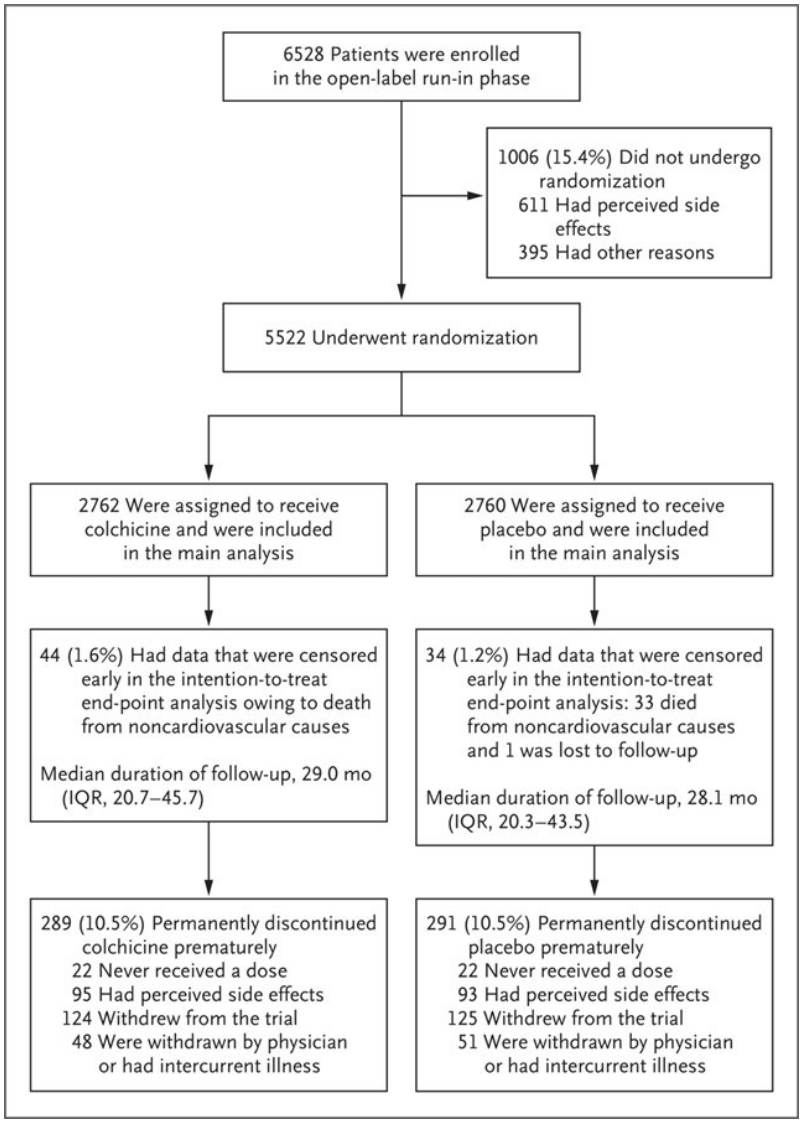
The study enrolled patients with evidence of coronary disease on coronary angiography, computed tomography angiography, or with significant coronary artery calcification (CACS > 400). Patients in the control group were on optimal medical therapy with antiplatelet, high-intensity statin therapy, and anti-ischemic agents.

Reviewer's comments: The study was appropriately enriched with patients with CAD and at risk for cardiovascular events. The inclusion of multiple modalities to identify patients with CAD allows for broader interpretation of study results as it reflects the diverse phenotype of patients with CAD seen in clinical practice.

Compliance with Good Clinical Practices

This was a literature-based review for the LoDoCo2 trial. The protocol for LoDoCo2 provides an attestation that the study was conducted according to the Study Protocol, current Declaration of Helsinki, the International Conference on Harmonization Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), Good Clinical Practice (GCP) guidelines, and according to the local guidelines, regulations and acts.

Figure 2: Patient Enrollment, Randomization, and Follow-up



(Source: LoDoCo2 Trial Protocol)

Key Inclusion and exclusion criteria for LoDoCo2 are highlighted below:

Inclusion criteria

1. Age >35 and <82 years
2. Proven coronary artery disease; as evidenced by coronary angiography, CT coronary angiography or a Coronary Artery Calcium Score (Agatston score >400). Individuals with a history of bypass surgery are only eligible if they have undergone coronary artery bypass surgery more than 10 years before, or have angiographic evidence of graft failure or have undergone percutaneous intervention since their bypass surgery
3. Clinically stable for at least six months

Exclusion criteria

1. Women who are pregnant, breast feeding or may be considering pregnancy during the study period.
2. Renal impairment as evidenced by a serum creatinine >150 μmol/l or estimated glomerular filtration rate (eGFR) <50mL/min/1.73m2
3. Severe heart failure – systolic or diastolic New York Heart Association Functional classification 3 or 4
4. Moderate or severe valvular heart disease considered likely to require intervention
5. Dependency or frailty or an estimated life expectancy < 5 years
6. Peripheral neuritis, myositis or marked myo-sensitivity to statins
7. Requirement for long term colchicine therapy for any other reason
8. Current enrollment in another trial

Dose selection:

The effects of colchicine on inflammatory biomarkers such as high-sensitivity C-reactive protein (hs-CRP) and IL-6 have been investigated in patients with stable CAD and heart failure. The dose studied in these trials were associated with lowering of the inflammatory biomarkers without significant adverse effects reported.[35,36]

One of the early assessments of the effect of colchicine in promoting the stability of an atherosclerotic plaque was in a small, short-term, open-label non-randomized study of patients with clinically stable coronary disease and high-sensitivity C-reactive protein (hs-CRP) ≥2.0 mg/L despite management with both aspirin and high-dose atorvastatin. These subjects who were without another proinflammatory co-morbidity to explain the elevated inflammatory biomarkers were administered colchicine 0.5 mg twice daily for 4 weeks with significant reduction in hs-CRP within weeks and no serious adverse effects were reported.
The effect of colchicine on levels of IL-6 have also been investigated in a prospective, randomized trial in patients with heart failure. Although the administration of colchicine 0.5mg twice daily did not lead to clinical improvement of heart failure symptomatology, it did reduce IL-6 and CRP after six months. Gastrointestinal intolerance occurred predominantly in the subjects randomized to treatment with colchicine with up to 9% of the colchicine arm discontinuing therapy. [37]

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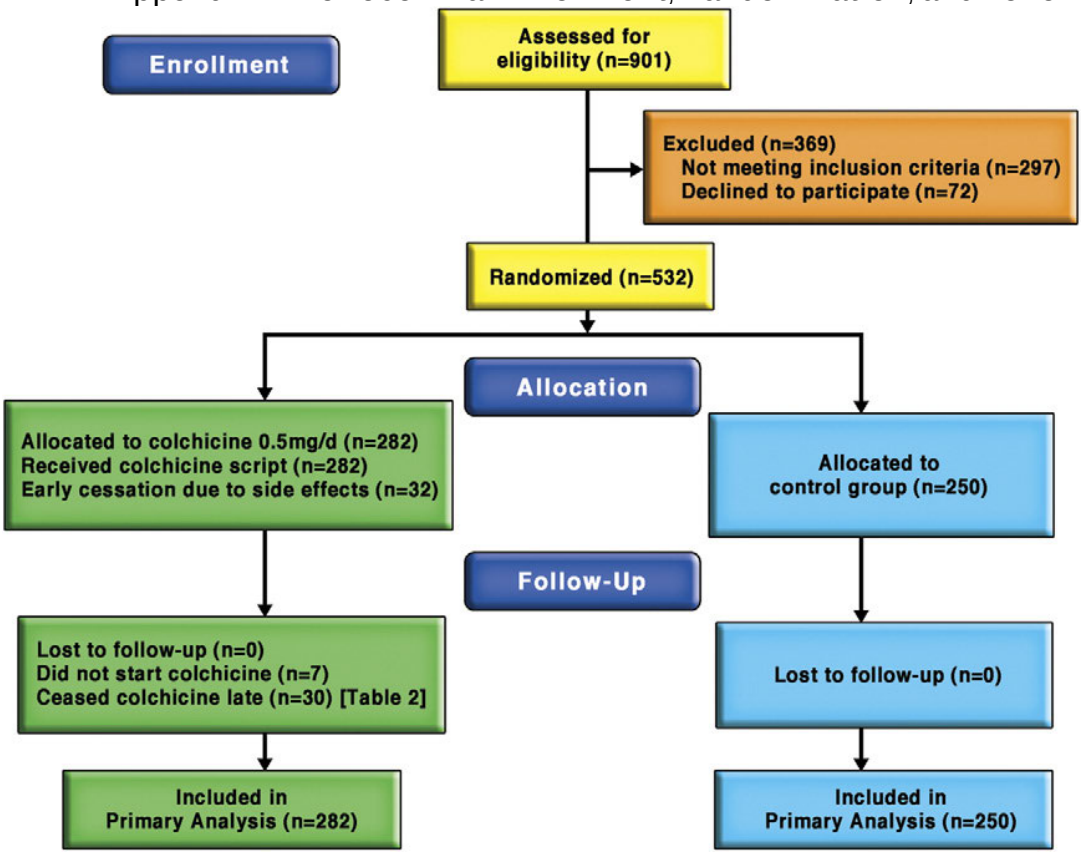
[35] Nidorf M, Thompson PL. Effect of colchicine (0.5 mg twice daily) on high-sensitivity C-reactive protein independent of aspirin and atorvastatin in patients with stable coronary artery disease. Am J Cardiol. 2007;99(6):805-807
[36] Deftereos S, Giannopoulos G, Panagopoulou V, et al. Anti-inflammatory treatment with colchicine in stable chronic heart failure: a prospective, randomized study. JACC Heart Fail. 2014;2(2):131-137
[37] Deftereos S, Giannopoulos G, Panagopoulou V, et al. Anti-inflammatory treatment with colchicine in stable chronic heart failure: a prospective, randomized study. JACC Heart Fail. 2014;2(2):131-137

In the proof-of-concept study (LoDoCo) preceding this trial, colchicine 0.5 mg tablet was administered once daily to a randomized cohort of 532 patients with stable coronary artery disease on optimal secondary prevention therapies for a median follow-up of 36 month (IQR, 24 -44 months). The study demonstrated a reduction in the primary composite incidence of acute coronary syndrome, out of hospital cardiac arrest, or noncardioembolic ischemic stroke, HR 0.33 (95% CI; 0.18, 0.59; p <0.001) number needed to treat (NNT= 11). The treatment effect was consistent in an ITT and on-treatment analysis.

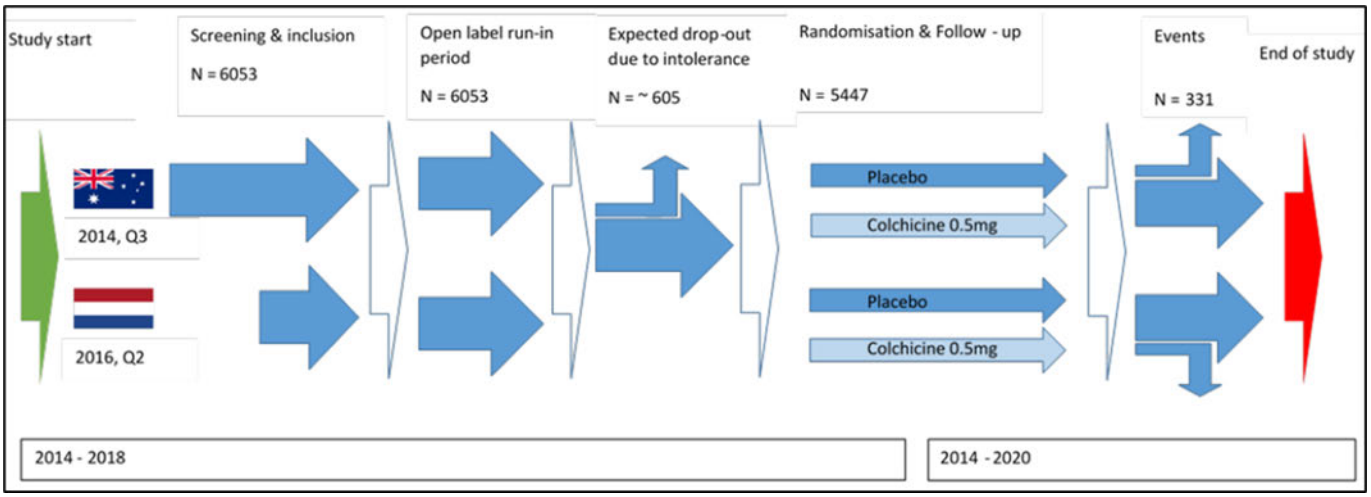
Appendix 1. LoDoCo Trial Enrollment, Randomization, and Follow-up.



Study Treatment

After a 30-day run-in period during which all study eligible subjects received open-label colchicine in addition to standard therapies for secondary prevention of CAD, subjects who tolerated and adhered to colchicine and remained clinical stable were randomized to either colchicine 0.5 mg tablets or matching placebo in a 1:1 fashion. Randomization was performed using a computerized algorithm to maintain concealment of treatment allocation. The study cohort was stratified according to country of enrollment.

Figure 3. LoDoCo 2 Study Design



(Source: LoDoCo2 Trial Protocol)

Study drug could be interrupted or discontinued at any time during the study by the patient, cardiologists, or other appropriate health care providers after consultation with the study coordinator.

Participants were allowed to withdraw from the study at any time, however efforts were made to follow all subjects randomized as they would have been in accordance with an intention to treat (ITT) principle.

Participants who discontinued study drug were allowed to resume at any time during the trial upon the approval of the study investigators. For participants who withdrew consent, discontinued study drug and/or study visits, efforts were made to maintain contact through the study period.

Subjects who could not be contacted after all reasonable efforts were exhausted were considered 'lost to follow-up' after the date of last recorded clinical contact. Premature or permanent discontinuation of colchicine or placebo was determined to have occurred if colchicine or placebo was permanently discontinued more than 30 days before the occurrence of a primary end-point event, the occurrence of non-cardiovascular death, or the end-of-trial date, whichever came first.

Adherence was monitored in both enrolling countries according to local standards. In Australia patients were questioned about adherence, however in The Netherlands drug accountability and pill counts were captured in the case report forms.

Reviewer's comments: While the use of a run-in period may be an appropriate design with an IP with a high rate of intolerance affecting adherence, it is always of concern if this approach exaggerates the treatment effect, introduces selection bias, and affects external validity. However, the totality of the evidence from the pivotal trial, supportive studies, and consistence of treatment effects with the ITT and "on treatment" analyses are reassuring.

All activities at participating sites in the trial were monitored for accuracy of documentation in the electronic case report forms, maintenance of patient records, adherence to protocol and handling of trial medications by dedicated monitors from the Working group on Cardiovascular Research the Netherlands (WCN) in The Netherlands and the Heart Research Institute (HRI) in Australia.

An independent Data Safety Monitoring Board (DSMB) composed of 5 members with representation in clinical trial methodology, cardiovascular disease, and biostatistics governed by the DSMB charter were involved in the monitoring of the LoDoCo2 Trial. An interim analysis for safety was performed after 75% of the primary outcomes were adjudicated for safety endpoints. A previously prespecified interim analysis for futility was eliminated based on published outcomes from a related trial that occurred during the LoDoCo2 trial.

Endpoints were adjudicated by an independent endpoint adjudication committee (EAC) formed to evaluate all reported clinical events in a blinded manner. The EAC members were clinicians with cardiovascular research experience. All adjudicated endpoints were performed according to predefined definitions documented in the endpoint adjudication charter (not available for review).

Reviewer's comments: While the DSMB charter, DSMB meeting minutes, EAC charter were not available for review with this NDA, the use of standardized definitions for end-point adjudication, composition of the DSMB board and absence of imbalance and close to 100% follow-up in trial results do not raise concerns about the trial result reliability.

Concomitant medications

Concomitant use of the following standard secondary prevention therapies was allowed in the trial. Allopurinol, diuretics, and medications indicated for the management of diabetes were also allowed.

- Antiplatelet therapy
- Anticoagulation, by vitamin K antagonist or direct oral anticoagulants
- Beta-blockers, calcium channel blockers
- Angiotensin-converting enzyme – inhibitors or angiotensin receptor
- blockers
- Lipid lowering drugs (statins, cholesterol uptake inhibitors, proprotein
- convertase subtilisin/kexin type 9 [PCSK9] inhibitors)

Appendix 2. Schedule of events LoDoCo2 Trial

Visit	V1	V2*	V3	V4	V5	V6	V7	V8	V9	EOS
Week	-4	0	26	52	78	104	130	156	182	global
Visit window (days)		-7/+7	+/- 14	+/- 14	+/- 14	+/- 14	+/- 14	+/- 14	+/- 14	-14+28
Obtain informed consent	x									
In- and exclusion criteria	x	x								
Relevant medical and cardiovascular history	x									
Renal function**	x									
Available laboratory data***§	x	x	x	x	x	x	x	x	x	x
Concomitant medication	x	x	x	x	x	x	x	x	x	x
Open label colchicine	x									
Dispense trial medication		x	x	x	x	x	x	x	x	
Questionnaires§	x	x	x	x	x	x	x	x	x	x
Healthcare costs§	x	x	x	x	x	x	x	x	x	x
Biomarker sub-study§¶										
Obtain informed consent	x									
Blood sampling	x	x		x						
Biobankingα										
Obtain informed consent										x
Blood sampling										x
Imaging sub-study §β										
Obtain informed consent										x
CCTA										x

** Renal function should not be older than six months at the moment of run-in (Source: LoDoCo2 protocol)
*** Assessed for routine out-patient clinical follow-up purposes or during hospitalization.
§ Only for the Dutch cohort.
¶ Max 300 patients
α Max 2500 patients
β Max 200 patients

Table 4: LoDoCo2 Trial End Points

Primary Endpoint 1. Composite of cardiovascular death, myocardial infarction, ischemic stroke or ischemia-driven coronary revascularization
Secondary Endpoints 2. Composite of cardiovascular death, myocardial infarction or ischemic stroke 3. Composite of myocardial infarction or ischemia-driven coronary revascularization 4. Composite of cardiovascular death or myocardial infarction 5. Ischemia-driven coronary revascularization 6. Myocardial infarction 7. Ischemic stroke 8. Death from any cause 9. Cardiovascular death
Additional Endpoints 10. Primary end point of the first LoDoCo trial: sudden cardiac death, non-fatal out of hospital cardiac arrest, acute coronary syndrome (myocardial infarction or unstable angina irrespective of revascularization), or atherosclerotic ischemic stroke 11. New onset or first recurrence of atrial fibrillation or atrial flutter 12. New onset diabetes 13. Deep vein thrombosis and/or pulmonary embolism 14. All myocardial infarction 15. Malignancies 16. Hospitalization for infections 17. Gout
Cardiovascular death is defined as any death with a clear relationship to underlying cardiovascular disease, including death secondary to acute myocardial infarction causing sudden death, or acute heart failure, a complication of a coronary revascularization procedure where the cause of death is clearly related to the procedure, death due to cardiovascular hemorrhage and death due to other cardiovascular causes. Myocardial infarction implies (biochemical) evidence of myocardial necrosis in a clinical setting consistent with myocardial ischemia. Myocardial typing is defined by the ACC/AHA/ESC 3rd universal definition of (acute) myocardial infarction. Myocardial infarction in the primary endpoint will include all nonprocedural MI's. i.e., Type 1, 2 and 4b myocardial infarction and type 3 as part of cardiovascular death Stroke is defined as symptoms of acute focal cerebral, spinal, or retinal dysfunction due to a vascular cause with other non-vascular etiologies excluded. The symptoms must last > 24 hours in the absence of brain imaging. The symptoms may last < 24 hours in the presence of pathological, imaging or other objective evidence of acute, focal cerebral, spinal, or retinal ischemia or hemorrhage. Ischemic stroke requires pathological, imaging, or another objective evidence of acute, focal cerebral, spinal, or retinal ischemic injury in a defined vascular distribution; or clinical evidence of acute, focal cerebral spinal cord, or retinal ischemic injury based on symptoms persisting > 24 hours or until death, and other etiologies excluded. Ischemic stroke includes hemorrhagic infarction but not intra-cerebral or subarachnoid hemorrhage. Ischemia-driven Coronary Revascularization includes all coronary revascularization that were performed in the context of myocardial infarction and those for worsening symptoms in combination with evidence of myocardial ischemia. The definition of the latter required the following:(1) A history of new or worsening symptoms consistent with myocardial ischemia that is not provoked by factors such as anemia, tachyarrhythmia, cold, unusual effort, sepsis or non-compliance with anti-anginal medication, (2) No documented rise in serum troponin suggestive of myocardial infarction, (3) Angiographic evidence of a culprit lesion, (4) Revascularization.

This was an event driven trial powered to detect a 30% reduction in the composite of cardiovascular death, spontaneous (nonprocedural) myocardial infarction, ischemic stroke, or ischemia- driven coronary revascularization. Based on the sponsors estimate of the annual primary composite endpoint event rate of 2.6% in the control group, and to account for the participants who would be intolerant to therapy and withdraw from the study, approximately 5,447 patients would need to be randomized to achieve 331 primary composite events over a median follow-up period of 3 years.

Statistical Analysis Plan

Recruitment started in August 2014 in Australia and October 2016 in The Netherlands. By 4th December 2018, 5,522 participants had been randomized in the trial. The Global End of Trial date as the 4th December 2019 being one year after randomization of the last participant. The SAP was finalized on 21st May 2020.

The first patient was enrolled in the LoDoCo2 trial on 4th August 2014. On 3rd November 2018 the last patient entered the open label run-in phase and on 3rd December 2018 the last patient was randomized. The last participant follow-up contact occurred on 17th February 2020. The database was locked on 22nd May 2020.

Analysis set

Full Analysis Set (FAS) – all randomized participants who took at least 1 tablet of their assigned trial medication. This population excludes 44 participants who were randomized after their open label run-in period that did not start trial medication. 5522 participants were randomized, of which 5478 participants started trial medication. The Full Analysis Set consists of these 5,478 participants.

Sample size determination

This is an event-driven trial. To detect hazard ratio of 0.7, 331 primary events would be required to provide >90% power, assuming a two-sided alpha level of 0.5 and an expected annual primary event rate of 2.6% in the placebo group and 10% of participants reporting early intolerance to therapy. Therefore, the trial aimed to enroll 6,053 screened patients, expecting 5,447 to be randomized and followed for a median of 3 years.

Analysis of primary and secondary endpoints

The primary and secondary endpoints are time-to-event outcomes, which were analyzed based on the Full Analysis Set.

A 2-sided log-rank test with stratification by region will be used to calculate p-values. Hazard ratios and 95% confidence intervals are obtained from Cox proportional hazards regression models with stratification by region (Western Australia and The Netherlands). Kaplan-Meier

estimates and curves of the cumulative risk of the outcome are used to depict the survival distributions in the two treatment groups.

Type I error control

If statistical significance for the primary outcome is achieved at alpha=0.05, the secondary outcomes are tested in a hierarchical fashion at the same alpha level.

Subgroup Analyses

The following subgroups will be analyzed:

- Age (≤ 65 years, > 65 years)
- Sex (Male, Female)
- Smoking Status (Yes, No)
- Diabetes at baseline (Yes, No)
- Insulin Use (Yes / No)
- Hypertension (Yes, No)
- Prior Acute Coronary Syndrome (Yes, No)
- Prior coronary revascularization (Percutaneous Coronary Intervention (PCI) and/or Coronary Artery Bypass Grafting (CABG)) (Yes, No)
- Atrial fibrillation (Yes, No)
- Renal Impairment (Stage 1,2 versus 3A)
- Statin use (40 mg atorvastatin equivalent or higher, < 40 mg atorvastatin equivalent dose / no statin)
- Ezetimibe (Yes, No)
- Region (Western Australia, The Netherlands)

Protocol Amendments

There were eight amendments to the original trial protocol. There is limited information on the details of the amendments, however where available, a summary of the proposed changes has been described below. The last protocol amendment was submitted on January 22, 2020, prior to unblinding of the data.

Appendix 3: Summary of Protocol Amendments to LoDoCo2 Trial

Protocol Amendment	Date	Summary of changes	Patient enrollment (%)
Amendment 1	18-MAY-2016*	1. Section '6.4 Summary of known and potential risks and benefits' in protocol version 2.1, 19 May 2016 has been affected in amendment 1 in The Netherlands.	N/A
Amendment 2	19-MAY-2016	1. Added additional safety information for the trial information for the Dutch sites, also distributed and effected in amendment 1 in Netherlands only	N/A

Amendment 3	20-SEP-2016	1. Name change 'Working group on Cardiovascular Research The Netherlands' to 'Dutch Network for Cardiovascular Research' 2. Typographical errors in the text have been corrected 3. Additional questionnaire will be administered in The Netherlands, the iPCQ, to assess productivity.	N/A
Amendment 4	09-JAN-2017	1. Typographical and style errors have been corrected 2. Relocated subchapter 'sample size calculation' to 4.4 (initially erroneously positioned in chapter 5), clarified the role of DSMB and methods of sample size calculation (no alterations in content) 3. Added adverse events of special interest (neuropathy and myopathy) in follow-up following the recommendation of the Dutch Medicines Evaluation Board. 4. Added assessments at baseline (questionnaires) in table view of assessments and broadened the time window of visit 2 (-7 + 7 days) and clarified differences in Dutch and Australian data collection 5. Clarified the possibility of a re-challenge during the run-in period and method of administration. 6. Clarified the necessity and definition of 'clinically stable' as conditions to randomize 7. Clarified methods of distribution of trial medicine in both countries 8. Clarified participating centers in Australia 9. Clarified handling of returned trial medication 10. Clarified unblinding procedures 11. Added data collection of the use of proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors following the recommendation of the RIVM 12. Renal function to be assessed within the last six months prior to the start of the open label run-in period 13. Estimated clearance to be registered following calculations used by the local lab (MDRD, CKDEPI, Cockcroft-Gault) 14. Clarified guidelines for study drug interruption and adjusted these to be in accordance with the patient information leaflet for Colchicine from Tiofarma: '…interruption might be considered when severe renal impairment occurs….' A clinically relevant cut-off for renal clearance of 30 ml/min/1.73m2 was chosen since guidelines, the patient information leaflets from Tiofarma, other manufactures and the Medicines Evaluation Board ('Farmacotherapeutisch Kompas') do not offer directives concerning cut-offs and the AKIN and RIFLE criteria for renal impairment are relative measures. 15. Clarified handling of patients lost to follow up 16. Clarified definition of serious adverse events, methods of expedited reporting and waiving reporting and unblinding when it concerns study outcomes 17. Changed methods and timing of interim analysis following the recommendation of the Dutch Medicines Evaluation Board. No interim analyses for efficacy will be done. Interim analyses for safety and futility are maintained, but at 75% of accrued events 18. Added biomarker sub-study following the recommendation of the Dutch Medicines Evaluation Board. In a subset of patients serial biomarkers of hematology, renal function, lipidology, glycemic and inflammatory status will be assessed to add surrogate markers to evaluate effect of colchicine and possibly elucidate mechanisms of action	N/A

		19. Changed endpoints and their order following the recommendation of the Dutch Medicines Evaluation Board and defined the endpoints more stringently • The primary endpoint changed to a composite endpoint consisting of cardiovascular death, first non-fatal acute coronary syndrome or non-fatal ischemic stroke • Secondary: the primary outcome from version 2.2 has become the first secondary outcome. Furthermore, the composite endpoint of cardiovascular death, myocardial infarction and ischemic stroke was added • All-cause mortality was added as fourth secondary endpoint • Tertiary: composite of atrial fibrillation and ischemic stroke was deleted • Clarified definitions of endpoints following the Endpoint Adjudication Charter • Clarified definition of primary and secondary endpoints • Clarified definition of diabetes • Clarified definition of deep vein thrombosis • Clarified definition of hospitalization • Clarified cost-effectiveness outcomes for the Dutch cohort only • Added events of special interest in definitions	
Amendment 5	01-JUN-2018	1. Adjusted study parameters • From an annual 3.5% to an annual 2.6% • From 4250 to 5447 randomized patients • From maximal 200 to maximal 500 participants in the laboratory sub-study • Extend recruitment range from 2014-2017 to 2014-2018 • Adjusted ratio of recruitment per country 2. Clarified routes of collection for routine laboratory measurements 3. Adjusted the order and phrasing of the secondary endpoints to suit the Endpoint Adjudication Charter (no changes in outcome assessment or content) 4. Added recurrent atrial fibrillation as exempted serious adverse event following the advice of the ethics committee 5. Added amendment 1 on trial medication safety as part of chapter 6.5 instead of as appendix with no alterations in content and added as part of this amendment list	N/A
Amendment 6	17-DEC-2018	1. Added process for global EOS date in timelines 2. Change in timing and content of interim analysis at 75% of adjudicated primary endpoints interim analysis will address safety only 3. Azithromycin added to list of macrolide antibiotics (CYP3A4 inhibitor) 4. GDPR statement on ethnicity data collection 5. Definition and typing of myocardial infarction specified 6. Myositis/ myopathy/ rhabdomyolysis classification updated	N/A
Amendment 7	20-AUG-2019	1. Typographical and style errors have been corrected 2. Rephrased acute coronary syndrome (myocardial infarction and unstable angina) in the primary outcome to myocardial infarction and ischemia-driven coronary revascularization (no changes in definition) following comments by peer review of the design of the protocol 3. Total number of randomized patients corrected 4. Added biobank at end of study 5. Added an imaging sub-study for selected participants 6. Added exploratory objectives 7. Changes in previous amendments have been clarified	N/A

Amendment 8	22-JAN-2020	1. Typographical and style errors corrected 2. Implementation of the End of Study window 3. Statistics- hierarchy of testing introduced 4. Statistics- Recurrent event analysis 5. Definition of endpoints introduced 6. Statistics- Hierarchy of secondary end points defined based on the observed blinded event rate in the cohort and the estimate of the (expected) treatment effect. 7. End points arranged as primary and secondary, including hierarchical and additional analyses. These changes proposed to align with the adjudication charter and statistical analysis plan. 8. Biobank substudy incorporated	N/A

6.2.2. Study Results

Baseline Characteristics

Baseline was defined as the last available measurement obtained prior to the start of the trial medication. Baseline renal function could be assessed within the six months leading to the run-in period.

Demographic and baseline characteristics appear to be balanced between the two study arms (Table 5). 85% of the cohort was male. The study was conducted completely outside of the United States. However, the standard of care for patients with ASCVD in the study sites are similar and relevant to patients in the United States. Most of the subjects had a prior history of acute coronary syndrome (84 %) with more than two-thirds of the events occurring greater than 24 months prior to randomization. Approximately 84% of the cohort had undergone prior coronary revascularization with 75 % being revascularized by percutaneous coronary intervention (PCI). 5 % of the cohort had mild to moderately reduced renal function (45-59 mL/min/1.73m^2) and 8% of the study population had a history of gout for which the IP is currently approved.

Risk factors for CAD was balanced across treatment groups. Over half of the study population had a history of hypertension at baseline, 12 % of the patients were smokers, and 18 % were being treated for diabetes mellitus.

Table 5: Baseline Demographics

Characteristic	Colchicine (N=2762)	Placebo (N=2760)
Age — yr	65.8±8.4	65.9±8.7
Female sex — no. (%)	457 (16.5)	389 (14.1)
Country — no. (%)		
Australia	951 (34.4)	953 (34.5)
The Netherlands	1811 (65.6)	1807 (65.5)
Current smoker — no. (%)†	318 (11.5)	330 (12.0)
Hypertension — no. (%)	1421 (51.4)	1387 (50.3)
Diabetes — no. (%)		
Patients receiving any treatment for diabetes	492 (17.8)	515 (18.7)
Patients dependent on insulin	140 (5.1)	147 (5.3)
Renal function — no. (%)‡		
Stage 1 or 2	2614 (94.6)	2602 (94.3)
Stage 3a	148 (5.4)	158 (5.7)
Prior acute coronary syndrome — no. (%)	2323 (84.1)	2335 (84.6)
Time since last acute coronary syndrome — no. (%)		
≤24 mo	753 (27.3)	726 (26.3)
>24 mo	1570 (56.8)	1609 (58.3)
Prior coronary revascularization — no. (%)	2301 (83.3)	2320 (84.1)
Coronary-artery bypass grafting	319 (11.5)	391 (14.2)
Percutaneous coronary intervention	2100 (76.0)	2077 (75.3)
History of atrial fibrillation — no. (%)	332 (12.0)	317 (11.5)
History of gout — no. (%)	220 (8.0)	226 (8.2)
Medication use — no. (%)		
Single antiplatelet therapy	1849 (66.9)	1852 (67.1)
Dual antiplatelet therapy	638 (23.1)	642 (23.3)
Anticoagulant	342 (12.4)	330 (12.0)
No antiplatelet agent or anticoagulant	4 (0.1)	11 (0.4)
Statin	2594 (93.9)	2594 (94.0)
Ezetimibe	551 (19.9)	522 (18.9)
Any lipid-lowering agent	2670 (96.7)	2665 (96.6)
Renin–angiotensin inhibitor	1995 (72.2)	1965 (71.2)
Beta-blocker	1692 (61.3)	1735 (62.9)
Calcium-channel blocker	633 (22.9)	611 (22.1)

* Plus–minus values are means ±SD.
† Information on smoking was missing for 21 patients.
‡ Stage 1 refers to an estimated glomerular filtration rate of at least 90 ml per minute per 1.73 m^2 of body-surface area (normal or high), stage 2 to a rate of 60 to 89 ml per minute per 1.73 m^2 (mildly decreased), and stage 3a to a rate of 45 to 59 ml per minute per 1.73 m^2 (mildly to moderately decreased). Stages are based on the Kidney Disease: Improving Global Outcomes (KDIGO) Clinical Practice Guideline for Acute Kidney Injury.[14]

When the baseline characteristics were stratified by country of enrollment, some imbalances were noteworthy. There were more smokers (16 %) versus (4 %), more patients with mild-moderate renal dysfunction (8%) versus (1%), prior CAD (86%) versus (80%), prior PCI (81%) versus (65%), in the Netherland cohort compared to Australia. Table 6 presents the baseline characteristics stratified by country of enrollment.

Appendix 4: Baseline Characteristics of the Trial Participants Stratified by Country

Characteristic	Australia (N=1904)	The Netherlands (N=3618)
Age – yr	67.1 ± 8.4	65.1 ± 8.6
Female sex – no. (%)	252 (13.2%)	594 (16.4%)
Current smoker – no. (%)†	80 (4.2%)	568 (15.7%)
Hypertension – no. (%)	1025 (53.8%)	1783 (49.3%)
Diabetes – no. (%)		
Any treatment	345 (18.1%)	662 (18.3%)
Insulin dependent – no. (%)	96 (5.0%)	191 (5.3%)
Renal function‡		
Stage 1, 2 – no. (%)	1884 (98.9%)	3332 (92.1%)
Stage 3a – no. (%)	20 (1.1%)	286 (7.9%)
Prior acute coronary syndrome – no. (%)	1532 (80.5%)	3126 (86.4%)
Time since last acute coronary syndrome		
≤ 24 months – no. (%)	385 (20.2%)	1094 (30.2%)
> 24 months – no. (%)	1147 (60.2%)	2032 (56.2%)
Prior coronary revascularization – no. (%)	1415 (74.3%)	3206 (88.6%)
Coronary artery bypass grafting – no. (%)	270 (14.2%)	440 (12.2%)
Percutaneous coronary intervention – no. (%)	1241 (65.2%)	2936 (81.1%)
History of atrial fibrillation – no. (%)	190 (10.0%)	459 (12.7%)
History of gout – no. (%)	162 (8.5%)	284 (7.8%)
Medication use		
Single antiplatelet therapy – no. (%)	1266 (66.5%)	2435 (67.3%)
Dual antiplatelet therapy – no. (%)	551 (28.9%)	729 (20.1%)
Anticoagulant – no. (%)	154 (8.1%)	518 (14.3%)
No antiplatelet agent or anticoagulant – no. (%)	4 (0.2%)	11 (0.3%)
Statin – no. (%)	1838 (96.5%)	3350 (92.6%)
Ezetimibe – no. (%)	221 (11.6%)	852 (23.5%)
Any lipid-lowering agent – no. (%)	1865 (98.0%)	3470 (95.9%)
Renin angiotensin inhibitor – no. (%)	1403 (73.7%)	2557 (70.7%)
Beta-blocker – no. (%)	991 (52.0%)	2436 (67.3%)
Calcium-channel blocker – no. (%)	466 (24.5%)	778 (21.5%)

* Plus-minus values are means and standard deviation.
† For 21 participants information on smoking was missing.
‡ Stage 1 refers to an estimated glomerular filtration rate of ≥ 90 ml/min per 1.73m2 (normal or high), stage 2 to 60-89 ml/min per 1.73m2 (mildly decreased), and stage 3a to 45-59 ml/min per 1.73m2 (mildly to moderately decreased). Stages are based on the Clinical Practice Guideline of Kidney Disease: Improving Global Outcomes (KDIGO) [2]

Concomitant medications

Concomitant use of standard medical therapy at baseline was balanced across treatment groups. At baseline, 90% of the patients were on either single or dual antiplatelet therapy, 84% on anti-ischemic pharmacotherapy, 97% were on lipid lowering agents, and 72 % on renin–angiotensin inhibitor therapy. When stratified according to country of enrollment, more patients were on antiplatelet therapy in the Australian cohort (95%) compared to the Netherlands (87%). However, more patients were on anticoagulation (14%) versus (8%) , and beta-blockers (67%) versus (52%) in the Netherland cohort compared to Australia (Table 5).

Patient Disposition

6528 patients underwent the informed consent process and entered the open-label run-in phase. 5522 patients underwent randomization and 5478 received one dose of the investigational drug product or placebo. The most common reason for screen failure (15%) were intolerance of colchicine during the open-label run-in phase. Of the patients who underwent randomization, 11 % in each treatment group permanently discontinued the investigational drug or placebo during the study period. The reasons for premature discontinuation of therapy were, 1% (never initiated treatment), 3% (side effects), 5% (withdrew from study) and 2% (withdrawn by the investigator or had an intercurrent illness). There were no imbalances based on the treatment arm. Last follow-up contact with patients enrolled in the LoDoCo2 trial occurred on February 17, 2020, and vital status information was available for all but one patient at the end of the follow-up period (Fig. 2).

Reviewer's comments: There was no data on the number patients who intermittently discontinued and resumed therapy (allowed in the protocol) during the study which could raise concerns for inadvertently unblinding treatment allocation during the study.

Protocol Violations/Deviations

There was no information provided in the published literature, supplementary data, or supporting documents addressing protocol violations/deviations that occurred during the LoDoCo2 trial.

Data Quality and Integrity

Efficacy Analysis

Median duration of follow-up in the study was 28.6 months (interquartile range, 20.5 to 44.4). Overall adherence with therapy is unknown. Adherence to IP was evaluated according to the local standards in Australia (patient reported) and The Netherlands (pill counts documented in the case report forms). However, patient level data is not available for review.

The protocol pre-specified approximately 331 adjudicated primary endpoint events of cardiovascular death, myocardial infarction, ischemic stroke or ischemia-driven coronary revascularization. A pre-specified interim analysis for futility was planned after 75% of the primary endpoints had been adjudicated, however this was canceled in the protocol amendment dated December 17, 2018.

Results of the composite primary event is shown below in Table 7. A hazard ratio of 0.69 indicated a statistically significant reduction in the first primary composite event for the patients randomized to treatment with colchicine when compared to placebo. The significant reduction in the composite events appears to be driven by a reduction in myocardial infarction HR 0.70 (95% CI: 0.53, 0.93) and ischemia-driven coronary revascularization HR 0.75 (95% CI: 0.60, 0.94). The treatment effect of colchicine on CV death was minimal but in favor of colchicine compared to the placebo arm. There were consistent reductions in events across every component of the composite primary endpoint (CV death, myocardial infarction, ischemic stroke or ischemia-driven coronary revascularization) in favor of colchicine versus placebo.

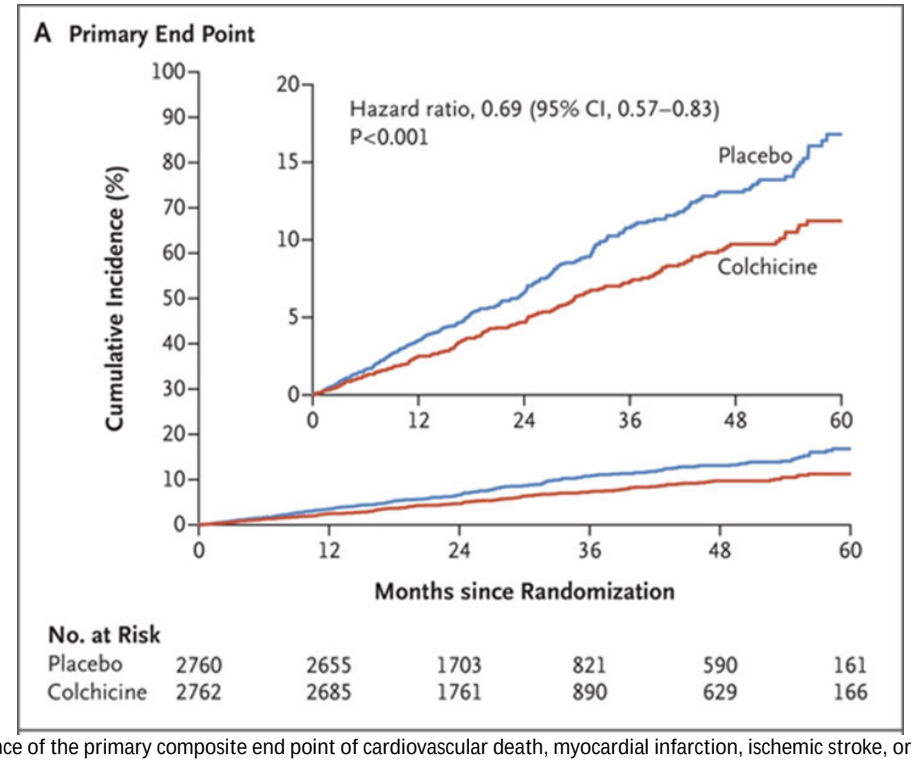
Table 6: Primary Outcome and Its components

	Colchicine (n=2762) (%)	Placebo (n=2760) (%)	HR (95% CI)	p-value
Primary outcome Cardiovascular death, myocardial infarction, ischemic stroke, or ischemia-driven coronary revascularization	187 (6.8)	264 (9.6)	0.69 (0.57 - 0.83)	<0.001
Components of primary outcome Cardiovascular death Myocardial infarction Ischemic stroke Ischemia-driven coronary revascularization	 20 (0.7) 83 (3.0) 16 (0.6) 135 (4.9)	 25 (0.9) 116 (4.2) 24 (0.9) 177 (6.4)	 0.80 (0.44 - 1.44) 0.70 (0.53 - 0.93) 0.66 (0.35 - 1.25) 0.75 (0.60 - 0.94)	

Reviewer's comments: An adequate scientific bridge was established between Lodoco and Colcrys based on two PK bridging bioequivalence (BE) studies (fast and fed) comparing Lodoco to Colgout tablets (one of the formulations used in the LoDoCo 2 trial), and a multimedia comparative in vitro dissolution data comparing LODOCO and Colcrys. The dissolution profile comparisons across all pH studied demonstrate rapid and similar dissolution (comparisons across all pH's demonstrate rapid and similar dissolution (> (b) (4) % release in 15 minutes). The sponsor did not evaluate the effects of weight as a surrogate for drug exposure on the treatment effect.

LoDoCo2 Trial studied a single dose level of colchicine irrespective of body weight. The plasma levels of colchicine in LODOCO2 would have largely overlapped with those resulting from administration of the approved 0.6-mg formulations marketed in the US. The differences in dose are, therefore, highly unlikely to have been consequential.

Figure 4: Kaplan-Meier Curves for the Cumulative incidence of the Primary Endpoint



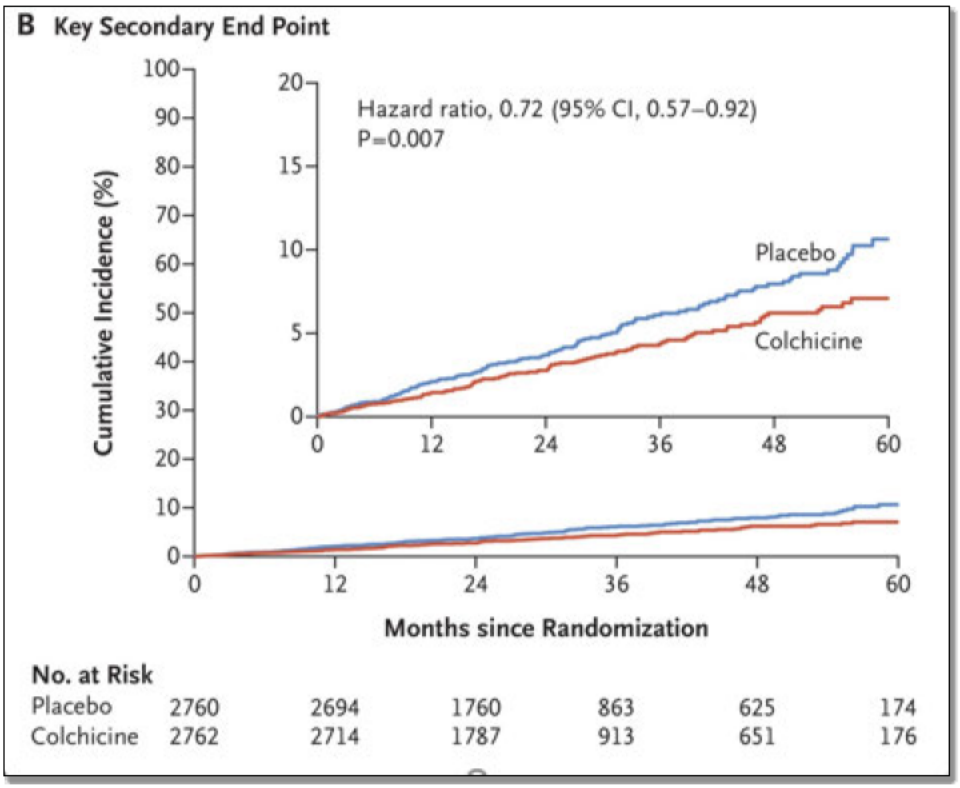
Cumulative incidence of the primary composite end point of cardiovascular death, myocardial infarction, ischemic stroke, or ischemia-driven coronary revascularization

There was a total of 187 total primary composite end-point events first events in the colchicine arm and 264 in the placebo arm. The treatment effect was consistently reproduced in the on-treatment analysis.

The benefit of colchicine in patients with stable CAD on standard secondary prevention therapies based on the cumulative incidence of the primary endpoint emerged early in the trial and persisted throughout the follow-up period.

Key secondary efficacy endpoint – composite of cardiovascular death, spontaneous myocardial infarction, or ischemic stroke occurred in fewer patients randomized to the colchicine arm, 115 patients (4.2%) compared to 157 patients (5.7%) in the placebo arm, with incidence rates of 1.5 and 2.1 events, respectively per 100 person-years (Fig. 6), HR 0.72 (95% CI,0.57, 0.92; p = 0.007). These effects were persistent throughout the duration of the study.

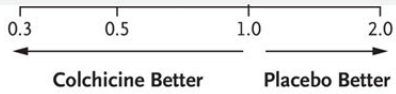
Figure 5: Kaplan-Meier Curves for the Cumulative incidence of the Key Secondary Endpoint



In the prespecified hierarchical testing of the ranked secondary end points, the incidence of the first five secondary end points were significantly lower in the colchicine group compared to placebo (Fig.7). The testing hierarchy for statistical significance was broken at the endpoint of ischemic stroke. These findings further support of the efficacy of colchicine in reducing the risk for cardiovascular events in patients with stable CAD.

Figure 6: Key Endpoints and their individual components

End Point	Colchicine (N=2762) no. of patients (%)	Colchicine (N=2762) no. of events/100 person-yr	Placebo (N=2760) no. of patients (%)	Placebo (N=2760) no. of events/100 person-yr	Hazard Ratio (95% CI)	P Value
Primary end point						
Cardiovascular death, myocardial infarction, ischemic stroke, or ischemia-driven coronary revascularization	187 (6.8)	2.5	264 (9.6)	3.6	0.69 (0.57–0.83)	<0.001
Secondary end points in ranked order						
Cardiovascular death, myocardial infarction, or ischemic stroke	115 (4.2)	1.5	157 (5.7)	2.1	0.72 (0.57–0.92)	0.007
Myocardial infarction or ischemia-driven coronary revascularization	155 (5.6)	2.1	224 (8.1)	3.0	0.67 (0.55–0.83)	<0.001
Cardiovascular death or myocardial infarction	100 (3.6)	1.3	138 (5.0)	1.8	0.71 (0.55–0.92)	0.01
Ischemia-driven coronary revascularization	135 (4.9)	1.8	177 (6.4)	2.4	0.75 (0.60–0.94)	0.01
Myocardial infarction	83 (3.0)	1.1	116 (4.2)	1.5	0.70 (0.53–0.93)	0.01
Ischemic stroke	16 (0.6)	0.2	24 (0.9)	0.3	0.66 (0.35–1.25)	0.20
Death from any cause	73 (2.6)	0.9	60 (2.2)	0.8	1.21 (0.86–1.71)	
Cardiovascular death	20 (0.7)	0.3	25 (0.9)	0.3	0.80 (0.44–1.44)	
Additional end points						
The primary end point in the first LoDoCo trial	201 (7.3)	2.7	290 (10.5)	4.0	0.67 (0.56–0.81)	
New onset or first recurrence in atrial fibrillation or atrial flutter	126 (4.6)	1.7	148 (5.4)	2.0	0.84 (0.66–1.07)	
Deep-vein thrombosis or pulmonary embolism or both	17 (0.6)	0.2	16 (0.6)	0.2	1.06 (0.53–2.10)	
Any myocardial infarctions	85 (3.1)	1.1	117 (4.2)	1.5	0.72 (0.54–0.95)	
New-onset diabetes	34 (1.2)	—	49 (1.8)	—	0.69 (0.44–1.06)	

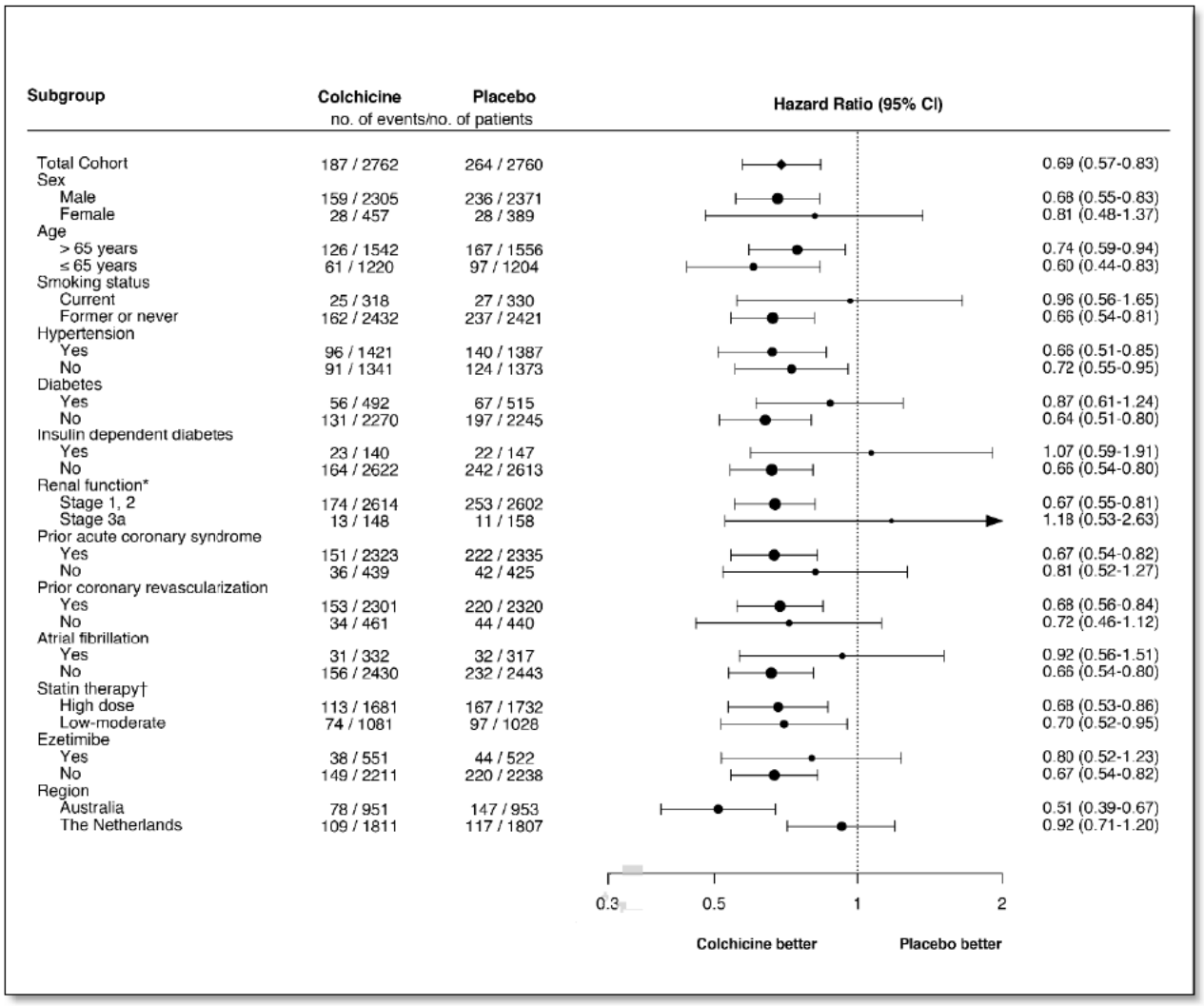


Subgroup Analyses

In subgroup analyses of the composite primary endpoint, the effects of colchicine were consistent in the pre-specified subgroups - demographics, medical history, and concomitant medications (Fig.8). In the subgroup of patients with mild to moderate renal insufficiency, and patients with diabetes requiring insulin, the effects of colchicine on the primary efficacy endpoint do not appear consistent with the primary efficacy endpoint. The reason for this is likely due to the small number of patients in the trial that are represented in these subgroups. Alternatively, colchicine is significantly excreted in urine and its clearance is decreased in patients with impaired renal function leading to a prolonged elimination half-life. The pharmacokinetics of colchicine in patients with impaired renal function could predispose these patients to the effects of colchicine toxicity and increase the risk for drug-drug interactions.

However, while some of the subgroups could be viewed as having little to no treatment effect, these results should be interpreted cautiously, recognizing that smaller subgroups are more sensitive to outliers.

Figure 7: Subgroup Analysis of the Primary Endpoint



The primary end point was cardiovascular death, myocardial infarction, ischemic stroke or ischemia-driven coronary revascularization.
*** Stage 1 refers to an estimated glomerular filtration rate of ≥ 90 ml/min per 1.73m2 (normal or high), stage 2 to 60-89 ml/min per 1.73m2 (mildly decreased), and stage 3a to 45-59 ml/min per 1.73m2 (mildly to moderately decreased). Stages are based on the Clinical Practice Guideline of Kidney Disease: Improving Global Outcomes (KDIGO).2**
† Statin intensity was categorized in accordance with the guidelines of the American College of Cardiology and American Heart Association.

Efficacy Results – Secondary and other relevant endpoints

Statistical reviewer's comment: The study LODOCO2 does show persuasive statistically significant overall treatment effect; however, the analyses were not verified by the statistical reviewer given that this is a literature-based application. The study result relies on published literature clinical studies, there were no discussion about the protocol and statistical analysis plan in the planning phase of the study, and no data were submitted to the agency, potential limitations could include lack of verification of efficacy results, lack of communication in conduct and plan of the study with the agency.

Additional Analyses Conducted on the Individual Trial

6.2.3. Review Issues Relevant to the Evaluation of Benefit

While no substantive review issues relevant to the evaluation of benefit of colchicine in reduction of cardiovascular events were identified during the review. The following additional comments were considered.

While the efficacy endpoints evaluated are clinically meaningful, the absence of concurrently obtained biomarker data in the entire cohort limits further insights into any mechanistic evidence to characterize the effects of colchicine in coronary artery disease . A biomarker substudy conducted in a subset of patients enrolled in the LoDoCo2 study was conducted but not reported in the trial. The findings of the substudy would provide additional insights into the mechanistic effects of colchicine in this patient population.

Another area of uncertainty is the lack of patient-focused clinical outcome assessments (COA) as part of this clinical trial. This precludes reliable assessment of the benefits on colchicine on patient's symptoms in alignment with the Agency's patient focused drug development initiative. Despite optimal implementation of guideline-directed pharmacotherapy and myocardial revascularization, a substantial proportion of patients with stable coronary artery disease continue to experience disabling symptoms. Refractory angina may be prevalent in up to 10% of patients with stable CAD and assessment of PROs in this trial would have been relevant to these patients.[38]

The review team concludes that colchicine is efficacious in reducing the composite of cardiovascular death, spontaneous (nonprocedural) myocardial infarction, ischemic stroke, or ischemia-driven coronary revascularization in patients with established atherosclerotic disease or with multiple risk factors for cardiovascular disease as demonstrated in the LoDoCo2 trial.

[38] Gallone G, Baldetti L, Tzanis G, et al. Refractory Angina. J Am Coll Cardiol Intv. 2020 Jan, 13 (1) 1–19

7. Review of Safety

Safety Review Approach

Colchicine was first approved in the US in 1961 as part of a combination drug product indicated for the treatment of gout. It has been commercially available for over 60 years in the United States and worldwide with a well characterized PK/PD profile and safety profile.

Colchicine is approved for the prophylaxis and treatment of gout in adults and for the treatment of Familial Mediterranean fever (FMF) in adults and children 4 years or older. It is approved for use at daily doses up to 1.8 mg (gout) and 2.4 mg (FMF). Colchicine acts in a dose-dependent manner, and most side effects reverse with lowering the dose or cessation of treatment.[39] To mitigate risks for toxicity, dosage adjustments are recommended for acutely ill patients with impaired renal function or body weight under 70 kg. There is substantial overlap between therapeutic doses and doses for which toxicity have occurred. Well described adverse events associated with colchicine use include gastrointestinal disorders (diarrhea, nausea, vomiting, abdominal discomfort), fatigue, headache, myopathy, elevated CPK, alopecia, maculopapular rash, and purpuric rash.[40]

Serious toxic manifestations associated with colchicine use include myelosuppression, disseminated intravascular coagulation and injury to cells in the renal, hepatic, circulatory and central nervous systems. Reports of fatalities associated with colchicine toxicity are rare in literature.

7.2. Review of the Safety Database

[39] Imazio M, Nidorf M. Colchicine and the heart. Eur Heart J. 2021;42(28):2745-2760.

[40] Andreis A, Imazio M, Avondo S, Casula M, Paneva E, Piroli F and De Ferrari GM. Adverse events of colchicine for cardiovascular diseases: a comprehensive meta-analysis of 14 188 patients from 21 randomized controlled trials. J Cardiovasc Med (Hagerstown) 2021;22:637–644

7.2.1. Overall Exposure

The safety review is based in part on the Applicant's reliance on FDA prior findings of safety for Colchicine, published literature, and two randomized controlled trials - LoDoCo and LoDoCo2 studies supporting the safety of colchicine for the proposed indication.
The Applicant has also pooled additional data from supportive studies, Australian COPS and Defteros et. al. for further assessment of the safety profile of Colchicine with long-term use.

Colchicine in Patients with Acute Coronary Syndrome (COPS) Trial was a multicenter, randomized, double-blind, placebo-controlled trial of adult (18-85 years) subjects with ACS and evidence of coronary artery disease on coronary angiography managed with either percutaneous coronary intervention or medical therapy. Subjects were assigned to receive either colchicine (0.5 mg twice daily for the first month, then 0.5 mg daily for 11 months) or placebo, in addition to standard secondary prevention pharmacotherapy, and were followed up for a minimum of 12 months. Dose reduction of study medication to once daily was permitted if participants developed severe gastrointestinal symptoms within the first month of treatment. The primary outcome was a composite of all-cause mortality, ACS, ischemia-driven (unplanned) urgent revascularization, and noncardioembolic ischemic stroke in a time to event analysis. At the end of the study period, 61 (15%) patients in the colchicine group had discontinued the study medication, compared with 33 (8%) patients in the placebo group. The main reasons for this were gastrointestinal intolerance (9% versus 4%) and personal choice (4% versus 2%) in the colchicine versus placebo groups respectively.

The pilot study of Anti-Inflammatory Treatment With Colchicine in Acute Myocardial Infarction (Deftereos et. al.), was a prospective, double-blinded, placebo-controlled study to test the hypothesis that a short course of colchicine treatment could lead to reduction in infarct size. Patients presenting with STEMI ≤12 hours from pain onset and treated with primary percutaneous coronary intervention were randomized (using a 1:1 allocation scheme) to colchicine or placebo for 5 days. (N = 77 receiving at least one dose of colchicine; N= 77 in the colchicine arm and N = 74 in the placebo arm). The primary outcome was the AUC of creatine kinase-myocardial brain (CK-MB) fraction concentration. Colchicine was administered as a loading dose of 2 mg (1.5 mg initially followed by 0.5 mg 1 hour later) and continuing with 0.5 mg twice daily, or placebo, for 5 days. Subjects who weighed < 60 kg body weight received 0.5 mg once daily. Monitoring of adverse events focused on gastrointestinal manifestations, hepatotoxicity, myelotoxicity, and myotoxicity. 151 patients underwent randomization and were included in the final analysis (77 in the colchicine group and 74 controls). 23 of 151 patients discontinued treatment before completion of the study. The discontinuation rate was 26% in the colchicine group (20 of 77 patients) versus 4% in the control group (3 of 74 patients; p<0.001). The reason for discontinuing the study drug include diarrhea in 16 of 23 cases (15 belonged to the colchicine group and 1 to the control group) and nausea/vomiting in 3 cases (all in the colchicine group). In 1 case, marked elevation in serum alanine aminotransferase was reported as the reason for study drug discontinuation (up to ≈5 times the upper reference limit,

without any sequelae). No cases of myelotoxicity were reported. In-hospital death occurred in 1 patient in the colchicine group and 1 patient in the control group (on days 4 and 5 of hospitalization, respectively).

Table 7. Incidence of Adverse Events in Individual Studies for Safety

Organ system	Adverse events (MeDRA terms)	LoDoCo2		COPS trials		Deftereos trial	
		Colchicine (N=2762) No. of patients (%)	Placebo (N=2760) No. of patients (%)	Colchicine (N=396) No. of patients (%)	Placebo (N=399) No. of patients (%)	Colchicine (N=77) No. of patients (%)	Placebo (N=74) No. of patients (%)
Gastrointestinal	Gastrointestinal symptoms including diarrhea, flatulence, and abdominal discomfort	-	-	91 (23.0)	83 (20.8)	-	-
	Diarrhea	-	-	-	-	15 (19.48)	1 (1.35)
	Nausea	-	-	-	-	3 (3.89)	-
Dermatology	Skin rashes	-	-	0	10 (2.6)	0	0
	Alopecia	-	-	0	1 (0.3)	-	-
Neuromuscular	Paresthesia	-	-	0	2 (0.5)	-	-
	Dysesthesia	143/1811 (7.9) *	150/1807 (8.3) *	-	-	-	-
	Myalgia	384/1811 (21.2) *	334/1807 (18.5) *	0	8 (2.0)	-	-
	Myotoxic effects/ Myelosuppression	3 (0.1)	3 (0.1)	0	0	-	-
	Neutropenia	4 (0.1)	3 (0.1)	-	-	-	-
Other	Gout	38 (1.4)	95 (3.4)	-	-	-	-

*In LoDoCo2 study, data were collected for the Netherlands cohort only. Reporting of these adverse events was requested by the Medicines Evaluation Board in the Netherlands when the trial was expanded to include patients from that country. Dysesthesia was verbatim used by the author for Paresthesia symptoms.
#The safety population was defined as patients who took at least one dose of colchicine or placebo.

No new colchicine associated risks were identified in the studies supporting the use of colchicine in coronary artery disease.

Gastrointestinal adverse effects the most common reported treatment emergent adverse effect with colchicine therapy resulting in premature discontinuation. Patients typically report diarrhea, nausea, or vomiting. These effects reverse with lowering the dose or cessation of treatment.

Myalgias were also reported in LoDoCo (1%) and LoDoCo 2 (21.2% in colchicine arm versus 18.5% in placebo). Of note, the data in LoDoCo 2 was exclusive to the Netherland cohort as this AE was not assessed in the Australia cohort. In the COPS trial, no patient in the colchicine

arm reported an AE of myalgias compared to 8 patients (2%) in the placebo arm. The use of statins were comparable in both studies.

Non-cardiovascular deaths occurred more frequently in the colchicine group in LoDoCo2 (53 patients (1.9%) in the colchicine arm versus 35 patients(1.3%) in the placebo arm, HR 1.51 (95% CI, 0.99, 2.31). A similar finding was also observed in the Australian COPs Trial (5 patients in the colchicine arm versus 0 in placebo; p=0.024). The small number of events, insignificant relative difference between the groups in both trials preclude conclusive discussion on this finding.

Reviewer's comments: There are no significant concerns regarding the safety database or with the additional studies submitted to support the safety assessment of the to-be marketed drug. While there are uncertainties about data fidelity with a literature-based review and without access to patient level data, these have uncertainties have a low impact in this review partly due to the absence of an imbalance in adverse events reported in the trial.

This risk of colchicine toxicity and drug-drug interaction will be described in the labeling which will include the dose limits for the proposed indication, drug-drug interactions, warning and precaution statements to mitigate the risk of colchicine toxicity.

7.2.2. Relevant characteristics of the safety population:

The safety assessment to support the use of colchicine in the reduction of cardiovascular events relies on LoDoCo and LoDoCo2 Trials. Additional supportive data from COPS2 Trial and Defteros trials were provided to the Applicant to support the safe of long-term colchicine for the prevention of cardiovascular events in patients with chronic coronary disease.

Table 8 Baseline demographics of patients in the pooled clinical studies for safety

Baseline characteristics	LoDoCo trial		LoDoCo2 trial		COPS trial		Deftereos trial	
	Colchicine (n=282)	Placebo (n=250)	Colchicine (n=2762)	Placebo (n=2760)	Colchicine (n=396)	Placebo (n=399)	Colchicine (n=77)	Placebo (n=74)
Mean Age (years)	66 ± 9.6	67 ± 9.2	65.8 ± 8.4	65.9 ± 8.7	59.7 ± 10.2	60.0 ± 10.4	58	58
Male no (%)	251 (89)	222 (89)	2305 (83.8)	2371 (85.9)	322 (81)	310 (78)	52 (68)	52 (70)
Female no (%)	31 (11)	28 (11)	457 (16.5)	389 (14.1)	86 (19)	89 (22)	25 (32)	22 (30)
BMI, kg/m^2	NA	NA	NA	NA	116 (29)	102 (26)	27.1	27.1

7.2.3. Adequacy of the safety database:

The median duration of exposure was 36 months (LoDoCo), 28.6 months (LoDoCo2), 12 months (COPS Trial). The safety database is considered adequate for a reasonable assessment of the safe use of colchicine long-term. 3386 subjects had exposure to colchicine for the proposed indication. 2990 of these subjects were exposed for longer than 24 months. There were no unexpected safety findings.

7.3. Adequacy of Applicant's Clinical Safety Assessments

7.3.1. Issues Regarding Data Integrity and Submission Quality

7.3.2. Categorization of Adverse Events

Adverse Events (AEs) was defined as any undesirable experience (either a medical occurrence or worsening of pre-existing medical condition) occurring to a subject during the study, whether it was considered related to the trial medication. AE reporting were deemed mandatory for the following subset of events.

- Non-serious adverse reactions leading to discontinuation of trial medication (adverse drug reaction)
- Non-serious AEs of special interest base on known safety profile of colchicine (Table 11)
- Serious adverse events (SAEs) - untoward medical occurrence that results in death, is life-threatening or results in persistent or significant disability/incapacity, requires inpatient hospitalization or causes prolongation of existing hospitalization, results in persistent or significant disability/incapacity or congenital anomaly/birth defect. SAE reporting was performed per ICH-GCP by the investigators within 24 hours of knowledge by the investigator team, to the project office. Expedited reporting to the authorities will be done by the respective project offices according to the local applicable guidelines.

Table 9. Adverse events of special interest

Adverse events of special interest	Definition
Neutropenia	Investigator-reported and defined as an absolute neutrophil count <1500/μL (<1.5 x 109/L).
Dysesthesia	Investigator-reported and defined as numbness, paraesthesia or allodynia in any dermatome. Queried at every clinical visit in the cohort from The Netherlands only.
Myalgia	Investigator-reported and defined as muscle complaints without elevated biomarkers. Queried at every clinical visit in the cohort from The Netherlands only.
Myotoxicity	Evaluated by a blinded, independent physician who assessed severity and relation to trial medication. It was classified as myalgia, myopathy, myositis or rhabdomyolysis, according to the European Atherosclerosis Society Consensus Panel Statement on Assessment, Aetiology and Management of Statin-associated muscle symptoms from 2015. [4]
Cancer	Evaluated by a blinded, independent physician of the End Point Adjudication Committee. Classified according to anatomic site of origin and whether it concerns a suspected relapse or new occurrence.

Based on the study design and endpoints, the following study outcomes were waived from unblinding and exempted from the expedited reporting but will be included in the final study report.

- Cardiovascular death
- Non-fatal acute coronary syndrome
- Non-fatal ischemic stroke
- Non-fatal out of hospital cardiac arrest
- New onset and recurrence of atrial onset fibrillation or atrial flutter
- New onset of diabetes mellitus
- Deep vein thrombosis and/or pulmonary embolism.

Suspected unexpected serious adverse reactions (SUSARs)

These adverse effects must meet the following conditions,

- The event must be serious
- There must be a certain degree of probability that the event is a harmful and an undesirable reaction to the IP, regardless of the administered dose (assessed by the principal investigator)
- The adverse reaction must be unexpected, and the nature and severity of the AE are not in agreement with the product information as recorded in the summary of product characteristics.

The expedited reporting will occur no later than 15 days after first knowledge of the adverse reactions in the local system. For fatal or life-threatening cases, the term will be maximal seven days for a preliminary report with another eight days for completion of the report.

7.3.3. Routine Clinical Tests

Due to the extensive clinical experience with the long-term use of low dose colchicine no additional diagnostic tests (i.e., blood testing) to assess pharmacodynamics or pharmacokinetic profile were planned as part of the LoDoCo2 trial.

7.4. Safety Results

Deaths

A total of 133 deaths occurred during the study. CV death was considered a component of the primary endpoint (LoDoCo2) and occurred in 45 subjects (20 deaths in the colchicine arm versus 25 deaths in the placebo arm) during the study period. In the LoDoCo trial, there were 14 deaths, 10 in the control group and 4 patients in the colchicine arm. Of the 10 control patients, 5 deaths were adjudicated as cardiovascular. All four deaths that occurred in the colchicine group were from non-cardiac causes.

Table 10: Incidence on non-cardiovascular deaths in LoDoCo and LoDoCo 2 studies

Study	Drug /dose	No. of patients died Non CVS
Low-Dose Colchicine for Secondary Prevention of Cardiovascular Disease (LoDoCo trials, non CVS death)	Colchicine 0.5 mg once daily along with statins	57
	Placebo	45

In LoDoCo2, non-cardiovascular deaths occurred more frequently among the patients who received colchicine than among those who received placebo, with incidence rates of 0.7 and 0.5 events, respectively, per 100 person-years (hazard ratio (HR) 1.51; 95% CI 0.99 - 2.31). While the difference in not statistically significant and could have occurred by chance, an alternate explanation can also not be ruled out. The individual causes of death (Table 13) do not provide much insight into a plausible mechanism for this observation.

Table 11: Summary of Non-cardiovascular Deaths in LoDoCo2

	Colchicine (N = 2762)	Placebo (N = 2760)
	no.	*no.*
Cancer	26	22
Infection	4	4
Respiratory failure	9	4
Multi-organ failure	3	2
Dementia	4	1
Accidental	2	2
Progressive renal failure	1	-
Suicide	1	-
Cerebral vasculitis	1	-
Intestinal ischemia	1	-
Unknown	1	-
Total	53	35

7.4.2. Serious Adverse Events

Overall, more subjects in the treatment arm had SAEs compared to placebo However, the relative difference between the groups are less than 0.5% indicating there were no imbalances in the SAEs.

Table 12: Adverse Events (LoDoCo 2 Trial) in the Intention-to-Treat Population

Event	Colchicine (N=2762)		Placebo (N=2760)		Hazard Ratio or Cumulative Incidence Ratio (95% CI)
	no. of patients/ total no. (%)	*no. of events/100 person-yrs*	*no. of patients/ total no. (%)*	*no. of events/100 person-yrs*	
Noncardiovascular death	53/2762 (1.9)	0.7	35/2760 (1.3)	0.5	1.51 (0.99–2.31)
Diagnosis of cancer	120/2762 (4.3)	1.6	122/2760 (4.4)	1.6	0.98 (0.76–1.26)
Hospitalization for infection	137/2762 (5.0)	1.8	144/2760 (5.2)	1.9	0.95 (0.75–1.20)
Hospitalization for pneumonia	46/2762 (1.7)	0.6	55/2760 (2.0)	0.7	0.84 (0.56–1.24)
Hospitalization for gastrointestinal reason	53/2762 (1.9)	0.7	50/2760 (1.8)	0.7	1.06 (0.72–1.56)
Gout	38/2762 (1.4)	—	95/2760 (3.4)	—	0.40 (0.28–0.58)
Neutropenia	4/2762 (0.1)	—	3/2760 (0.1)	—	NR
Myotoxic effects†	3/2762 (0.1)	—	3/2760 (0.1)	—	NR
Myalgia‡	384/1811 (21.2)	—	334/1807 (18.5)	—	1.15 (1.01–1.31)
Dysesthesia¦ numbness or tingling‡	143/1811 (7.9)	—	150/1807 (8.3)	—	0.95 (0.76–1.18)

* Hazard ratios are reported for noncardiovascular death, diagnosis of cancer, hospitalization for infection, hospitalization for pneumonia, and hospitalization for gastrointestinal reason; cumulative incidence ratios are reported for gout, myalgia, and dysesthesia because time-to-event data were not collected for these end points. Cumulative incidence ratios are not reported (NR) for neutropenia and myotoxic effects because of the low numbers of events.
† Rhabdomyolysis occurred in one patient in the colchicine group, who had a full recovery.
‡ Data were collected for the Netherlands cohort only. Reporting of these adverse events was requested by the Medicines Evaluation Board in the Netherlands when the trial was expanded to include patients from that country.

7.4.3. Significant Adverse Events

Treatment Emergent Adverse Events and Adverse Reactions

Subjects in the LoDoCo and LoDoCo2 trials received Colchicine 0.5 mg Tablets daily over a median exposure period of 36 (24 – 44), and 28.6 (20.5 – 44.4) months respectively. The trial population were from Australia and Netherlands predominantly. Baseline characteristics have been previously described.

Gastrointestinal disorders were the most observed adverse reaction with Colchicine. In the LoDoCo trial 11 % of the study subjects reported early intolerance due to gastrointestinal side effects (Table 15). In LoDoCo 2 trial, of the 11% who prematurely discontinued the IP, one-third was for perceived side effects (Table 15). Other adverse events reported include myalgias, dysesthesia, hospitalization for infections, pneumonia, malignancies, and neutropenia (Table 14).

Table 13: Withdrawal from Therapy -LoDoCo

Early withdrawals	32 (11)
Late withdrawals*	30 (11)
Unrelated intercurrent illness	11 (3.9)
Patient choice	5 (1.8)
Perceived side effects	
Intestinal upset	7 (2.5)
Myalgia	2 (0.90)
Myositis	1 (<0.5)
Rash	1 (<0.5)
Alopecia	1 (<0.5)
Itch	1 (<0.5)
Peripheral neuritis	1 (<0.5)

Values are n (%). *Withdrawals after 30 days; average time to withdrawal was 2.36 years.

Laboratory Findings

N/A

7.5. Analysis of Submission-Summary of Safety Findings

Overall, there are no unexpected safety signals in this study.

- While non-cardiovascular deaths were higher in the colchicine arm compared to placebo, the risk difference was less than 1 %
- Adverse events of special interest with RD greater than 1% were myalgias (2.7%). There

were no concerning imbalances in AESIs

7.6. Safety Analyses by Demographic Subgroups

N/A

7.7. Specific Safety Studies/Clinical Trials

The Applicant has requested a full waiver for pediatric studies according to the agreed initial Pediatric Study Plan (iPSP) for pediatric patients from birth to less than 18 years on the grounds that necessary studies are impossible or highly impractical and the product fails to represent a meaningful therapeutic benefit over existing therapies for pediatric patients and is unlikely to be used in a substantial number of all pediatric age groups or the pediatric age group(s) for which a waiver is being requested.

7.8. Additional Safety Explorations

7.8.1. Human Carcinogenicity or Tumor Development

N/A

8. Labeling Recommendations

8.1.Prescription Drug Labeling

AGEPHA Pharma Middle East Trading, LLC submitted NDA 215727 for Lodoco (colchicine) tablets, 0.5 mg on April 13, 2022. The Agency issued a Refuse-to-File (RTF) letter to Agepha on June 11, 2022, based on inadequate information provided to support the nonclinical sections of the proposed Prescribing Information. The New Drug Application (NDA) 215727 for LODOCO (colchicine) tablets was resubmitted under a (505) (b)(2) regulatory framework in response to the Agency's Refuse to File letter dated June 11, 2022.

The reference list drug (RLD) for this submission is NDA 022352 for COLCRYS (colchicine, USP) tablets. The proposed indication sought for LODOCO (colchicine) tablets is to reduce the risk of myocardial infarction (MI), stroke, coronary revascularization, (b) (4) , and cardiovascular death among patients with established atherosclerotic disease or with multiple risk factors for cardiovascular disease.

This NDA relies in part on FDA's finding of safety for colchicine based on the listed drug, Colcrys (NDA 22352) and on published literature.
The proposed labeling from the resubmitted NDA dated September 20. 2022 was reviewed in

conjunction with Division of Medical Policy Programs (DMPP), and the Office of Prescription Drug Promotion (OPDP), and other applicable review disciplines.

Appropriate patent certifications and method of use statements were also submitted to the NDA.

Recommendations regarding the following sections of the NDA were issued to the Sponsor to address, revise, or edit based on the RLD, literature evidence, and safety data from the LoDoCo and LoDoCo 2 studies that inform the Warning and Precaution Session, drug-drug interactions, Container Labels & Carton Labeling.

Labeling negotiations between relevant disciplines within the FDA and the Sponsor occurred to arrive at the final acceptable labeling for the IP.

9. Risk Evaluation and Mitigation Strategies (REMS)

Colchicine has been used clinically worldwide as a single drug entity for over 70 years and its mechanisms of effect and pharmacokinetic profile have been well documented.

This NDA is being submitted under 505(b)(2) of the Federal Food and Drug Act with Colcrys tablets (Colcrys NDA 022352) as the reference listed drug (RLD). This application therefore, relies in part on the Agency's prior approval of the Colcrys NDA to support the nonclinical, clinical pharmacology and safety aspects of this NDA.

The daily dose exposure for the proposed indication (0.5 mg daily) is well below the daily dosage limits in currently approved indications – Gout and FMF and LoDoCo 2 trial had a median duration of follow-up of 28.6 months with end-point status was available for all but one patient.

The adverse events in the ITT population did not reveal a concerning safety signal that would require a risk evaluation and mitigation strategy for safe use.

The safety concerns will be addressed in the labeling.

10. Post marketing Requirements and Commitments

N/A

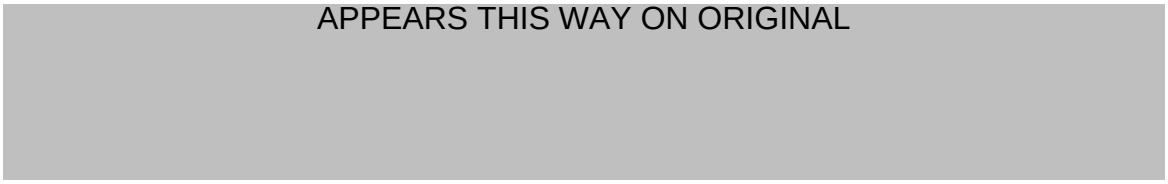
11. Appendices

11.1. Financial Disclosure

Covered Clinical Study (Name and/or Number): LoDoCo2 Trial

Was a list of clinical investigators provided?	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: >100 (LoDoCo 2 Protocol)		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): N/A		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): N/A		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) N/A_____		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

The Sponsor (Agepha) has provided Financial Certification and Disclosure statements for the clinical investigators who participated in the Bioavailability/Bioequivalence clinical study conducted at Axis Clinicals Limited, Ahmedabad.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