

***Murray & Poole Enterprises,
Ltd. v. Institut de Cardiologie
de Montréal,
No. IPR2023-01064***

Inter Partes Review of U.S. Patent No. 11,400,063

Presentation of Patent Owner Institut de Cardiologie de Montréal

October 15, 2024

Summary of Argument

- Background of relevant art, the '063 patent, and Dr. Tardif's surprising discovery.
- Relevant claim terms should be construed consistent with the intrinsic evidence.
- Ground 1: Bouabdallaoui (EX1005) is not prior art and therefore cannot anticipate.
- Ground 4: Claims 1-26, 28, and 45 are not obvious because EX1005 is not prior art and COLCRYs label (EX1016) fails to render claims obvious.
- Ground 2: Claims 27, 29-36, and 39 are not anticipated by COLCOT (EX1006).
- Ground 3: Claims 1-50 are not obvious over Nidorf (EX1007); EX1006; ESC Guidelines (EX1009); and EX1016, and Petitioner relies on hindsight bias.

Colchicine - Background

Colcrlys Label

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use COLCRYS[™] (colchicine, USP) tablets safely and effectively.

COLCRYS[™] (colchicine, USP) tablets
Initial U.S. Approval: 1961

INDICATIONS AND USAGE
COLCRYS (colchicine, USP) tablets are an alkaloid indicated for:

- gout flares (1.1)
 - Familial Mediterranean fever (FMF) in adults and children 4 years or older (1.2).
- COLCRYS is not an analgesic medication and should not be used to treat pain from other causes.

DOSAGE AND ADMINISTRATION
Gout Flares: 1.2 mg (2 tablets) at the first sign of a gout flare followed by 0.6 mg (1 tablet) one hour later (2.1).

FMF: Adults and Children older than 12 years 1.2 – 2.4 mg; Children 4 to 12 years 0.9 – 1.8 mg; Children 4 to 6 years 0.3 – 1.8 mg. (2.2, 2.3).

WARNINGS
Fatal overdose have been reported. Keep COLCRYS out of the reach of children. Blood dyscrasias: myelosuppression, thrombocytopenia, and aplastic anemia. Monitor for toxicity and if pre-discontinuation of colchicine is required.

Drug interaction P-gp and/or strong CYP3A4 inhibitors and death (5.3, 7).
Neuromuscular toxicity: Myopathy, especially in combination with statins. Consider temporary interruption or discontinuation of COLCRYS (5.4, 7).

FULL PRESCRIBING INFORMATION: CONTENTS*

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ADVERSE REACTIONS
Gout Flares: Most common adverse reaction is diarrhea (23%) and

COLCRYS[™] (colchicine, USP) tablets for Oral use
Initial U.S. Approval: 1961

INDICATIONS AND USAGE
COLCRYS (colchicine, USP) tablets are an alkaloid indicated for:

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- Familial Mediterranean fever (FMF) in adults and children 4 years or older (1.2).

COLCRYS is not an analgesic medication and should not be used to treat pain from other causes.

DOSAGE AND ADMINISTRATION

Gout Flares: 1.2 mg (2 tablets) at the first sign of a gout flare followed by 0.6 mg (1 tablet) one hour later (2.1).

FMF: Adults and Children older than 12 years 1.2 – 2.4 mg; Children 6 to 12 years 0.9 – 1.8 mg; Children 4 to 6 years 0.3 – 1.8 mg. (2.2, 2.3).

- Give total daily dose in one or two divided doses (2.2).
- Increase or decrease the dose as indicated and as tolerated in increments of 0.3 mg/day, not to exceed the maximum recommended daily dose (2.4).

See full prescribing information for dose adjustment regarding patients with impaired renal function (2.5) or hepatic function (2.6).

2 DOSAGE AND ADMINISTRATION

The long term use of colchicine is established for FMF but the safety and efficacy of repeat treatment in gout flares has not been evaluated. The dosing regimens for COLCRYS are different for the two indications and must be individualized.

The recommended dosage of COLCRYS depends on the patient's age, renal function, hepatic function, and use of other co-administered drugs [see *Dose Modification for Co-administration of Interacting Drugs* (2.4)].

COLCRYS tablets are administered orally, without regard to meals.

COLCRYS is not an analgesic medication and should not be used to treat pain from other causes.

2.1 Gout Flares

The recommended dose of COLCRYS for treatment of a gout flare is 1.2 mg (2 tablets) at the first sign of the flare followed by 0.6 mg (1 tablet) one hour later. Higher doses have not been found to be more effective.

The maximum recommended dose for treatment of gout flares is 1.8 mg over a 1 hour period.

2.2 FMF

The recommended dosage of COLCRYS for FMF in adults is 1.2 mg to 2.4 mg daily. COLCRYS should be increased as needed to control disease and as tolerated in increments of 0.3 mg/day to a maximum recommended daily dose. If intolerable side effects develop, the dose should be decreased in increments of 0.3 mg/day. The total daily COLCRYS dose may be administered in one to two divided doses.

Colchicine – Prior Attempts to Treat CV Conditions Failed

O'Keefe 1992

JGIM 1992;1597-1600

1597

Ineffectiveness of Colchicine for the Prevention of Restenosis After Coronary Angioplasty

JAMES H. O'KEEFE
TIMOTHY M. BART
ROBERT W. LIGGETT
Kansas City, Missouri

Colchicine, an antimitotic agent, has been shown to inhibit restenosis after coronary angioplasty in animal models. A prospective trial was conducted in a 2:1 fashion. Patients were randomized to receive either 0.6 mg twice daily (120 mg total) or placebo for 6 months after elective coronary angioplasty. Compliance with prescribed pills was similar in colchicine- and placebo-treated patients. The dropout rate in the colchicine group was 14.5% (74%) with angiographic measurements.

All currently available revascularization (including laser photocoagulation and percutaneous transluminal angioplasty) involves myointimal hyperplasia and significant restenosis by 6 months after angioplasty. The pathologic process involves rheologic factors in addition to the inflammatory response. The current study was performed to date has been the first to evaluate the effect of a single pharmacologic agent on restenosis rate after coronary angioplasty.

This exuberant, ma-

From the Mid America Heart Institute, Kansas City, Missouri. This study was presented at the American College of Cardiology, San Francisco, California, 1991. Manuscript received September 4, 1991; revised manuscript received December 4, 1991; accepted January 3, 1992.

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0735-1097/92/55.00

Discussion

Previous studies. In the current study, treatment with oral colchicine that was started at the time of coronary angioplasty had no effect on the subsequent rate of restenosis after angioplasty. In another trial (16) using colchicine preliminary results were also negative, although that trial used clinical nonangiographic end points. Although colchicine was demonstrated to be effective in reducing intimal proliferation after balloon injury to a rabbit iliac artery (14), the effect was apparent only with the highest dose of the medication. In that study, Currier et al. (14) found a reduced rate of restenosis in animals treated with high dose (0.2 mg/kg per day) but not with low dose (0.02 mg/kg per day) colchicine.

with incipient hepatic cirrhosis (15). Colchicine has not been used previously in a clinical trial for the prevention of restenosis after coronary angioplasty.

- Effectiveness of colchicine in CV setting found effective only at dangerously high dosages in animal models.
- At relatively safe dosage of 1.2 mg/day, was ineffective on reducing rate of restenosis after angioplasty.

Problems with Low-dose Colchicine CV Treatment

EX2054

J Thromb Thrombolysis (2012) 33:88–94
DOI 10.1007/s12294-011-9637-y

Effect of colchicine compared with placebo on high sensitivity C-reactive protein in patients with acute coronary syndrome or acute stroke: a pilot randomized controlled trial

Nina C. Raju · Qilong Yi · Mark Nidorf ·
Nick D. Fagel · Rajesh Hirahar · John W. Eikelboom

In summary, our pilot study provides no evidence that low-dose colchicine initiated after admission to hospital with an acute atherothrombotic vascular event either suppresses hs-CRP or affects platelet function at 30 days. Additional studies evaluating colchicine [17] and novel anti-inflammatory therapies [18–20] in patients with chronic atherothrombosis are ongoing and will further clarify the role of anti-inflammatory treatments for the prevention of cardiovascular events.

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Introduction

Cardiovascular disease is expected to remain the leading cause of death worldwide during the next two decades despite the widespread use of effective primary and secondary preventive strategies [1]. One approach to further reduce the risk developing cardiovascular disease and prevent its complications is to identify and treat new or emerging risk factors.

Inflammation plays a central role in the pathogenesis of atherosclerosis [2]. Damage to the vascular endothelium by established cardiovascular risk factors such as

MHI EXHIBIT 2054

EX1028

Clinical Investigation

The Low Dose Colchicine after Myocardial

This was an investigator initiated randomized, double-blind placebo controlled clinical trial. Patients were randomized in a 1:1 ratio to receive either colchicine 0.5 mg once daily or matched placebo for 30 days. Adult (>18 years old) patients were eligible for enrolment if they had sustained a type 1 acute MI (by the 3rd universal definition¹⁶) within the prior 7 days. All patients were recruited at Royal Perth Hospital, Perth, Western Australia.

dose colchicine was well tolerated and did not reduce compliance with other secondary preventative medications at 30 days.
Conclusion Treatment with low dose colchicine was safe and well tolerated, but was not associated with a significantly increased likelihood of achieving a CRP level <2 mg/L or lower absolute levels of CRP 30 days after an acute MI. (Am Heart J 2019;215:62-9.)

Inflammation is central to the pathogenesis of atherosclerosis and its acute manifestations.^{1,3} Likewise, patients with higher levels of the inflammatory biomarker C-reactive protein (CRP) 30 days following an acute myocardial infarction (MI) are at increased risk of

recurrent infarction and death due to coronary heart disease (CHD).⁴ It has been hypothesized, therefore, that therapies that specifically target inflammatory pathways might reduce recurrent vascular events in this setting. One such approach is to target specific proinflammatory

Conclusion Treatment with low dose colchicine was safe and well tolerated, but was not associated with a significantly increased likelihood of achieving a CRP level <2 mg/L or lower absolute levels of CRP 30 days after an acute MI. (Am Heart J 2019;215:62-9.)

<https://doi.org/10.1016/j.amh.2019.06.001>

agents available and has been used for decades to treat

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MURRAY & POOLE EXHIBIT 1028

Prior Art Studies Found Low-Dose Colchicine Not Effective in CV

EX2009

BMJ 2009;339:b2009

Ineffectiveness of Colchicine for the Prevention of Restenosis After Coronary Angioplasty

JAMES H. O'KEEFE, JR., MD, FACC, BEN D. MCCALLISTER, MD, FACC, TIMOTHY M. BATEMAN, MD, FACC, DEBORAH L. KUHNLEIN, RN, ROBERT W. LIGON, MA, GEOFFREY O. HARTZLER, MD, FACC Kansas City, Missouri

Colchicine, an antineoplastic agent, has shown promise in preventing restenosis after coronary angioplasty in experimental animal models. A prospective trial was conducted involving 197 patients randomized to a 2.5 mg tablet to treatment with oral colchicine, 0.5 mg twice daily (30 patients), or placebo (67 patients) for 6 months after elective coronary angioplasty. Treatment in all patients began between 12 h before angioplasty and 24 h after angioplasty. Compliance monitoring revealed that 96% of all prescribed pills were ingested. Demographic characteristics were similar in colchicine- and placebo-treated groups. A mean of 2.7 lesions/patient were dilated. Side effects resulted in a 6.6% dropout rate in the colchicine-treated patients.

Complete quantitative angiographic follow-up was obtained in 145 patients (74%) with 352 dilated lesions. Quantitative angiographic measurements were obtained in two orthogonal views at

baseline before angioplasty and immediately and at 6 months after angioplasty. The quantitative mean lumen diameter stenosis before angioplasty was 47% both in the 152 lesions in the placebo-treated group and in the 241 lesions in the colchicine-treated group; this value was reduced to 24% immediately after angioplasty in the lesions in both treatment groups.

At the 6-month angiogram, lesions had restenosed to 47% lumen diameter narrowing in the placebo-treated group compared with 46% in the colchicine-treated group ($P = .70$). Forty percent of colchicine-treated patients developed restenosis in at least one lesion compared with 45% of the placebo-treated group ($P = .55$). In conclusion, colchicine was ineffective for preventing restenosis after coronary angioplasty.

(*J Am Coll Cardiol* 1992;19:1597-1600)

All currently available methods for percutaneous coronary revascularization (including balloon dilation, atherectomy, laser photocoagulation and intracoronary stenting) cause significant endothelial trauma. The subsequent reparative response involves myointimal proliferation that results in a significant narrowing or restenosis in 30% to 40% of lesions by 6 months after angioplasty (1). The stimuli for the smooth muscle cell proliferation involve mechanical and rheologic factors in addition to heterogeneous growth factors emanating from inflammatory cells and elements of the coagulation system (2,3). The majority of restenosis trials performed to date have attempted to modify a single component of this complex redundant system. The failure of any single pharmacologic agent to consistently reduce the restenosis rate after coronary angioplasty is somewhat predictable in this context.

This exuberant, maladaptive smooth muscle cell prolifer-

ation has prompted some investigators to liken restenosis to a neoplastic process (4,5). The term "malignant restenosis" has been used to describe a syndrome characterized by rapid, refractory recurrences after repeated attempts at percutaneous coronary revascularization. When viewed from this perspective, the use of antineoplastic or antiproliferative agents is one of the most promising avenues of exploration in the search for a solution to the complex problem of restenosis.

Colchicine is an antineoplastic agent that binds to tubulin, disrupting spindle formation and resulting in the metaphase arrest of cell division. Colchicine has been shown to inhibit chemotaxis (7,8), collagen formation (9), muscle cell proliferation and platelet aggregation (10,11). In experimental animal models, this agent has prevented or reduced the formation of atherosclerotic plaques (12,13). Colchicine has also been effective in preventing myointimal proliferation after balloon arterial injury of the iliac artery in an atherosclerotic rabbit model (14) and has been reported to be effective in reducing fibroblastic proliferation in a patient with incipient hepatic cirrhosis (15). Colchicine has not been used previously in a clinical trial for the prevention of restenosis after coronary angioplasty.

From the Mid-America Heart Institute, St. Louis (H. O'Keefe, Jr., MD, Kansas City, MO, Missouri). This study was presented in part at the 49th Annual Meeting of the American College of Cardiology, New Orleans, Louisiana, March 1997.

Manuscript received September 4, 1991; revised manuscript received December 4, 1991; accepted January 1, 1992.

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0735-1057/92/09-1597-08

EX2054

J Thromb Thrombolysis 2002;13:555-564

DOI: 10.1081/JAT.2001.4007-7

Effect of colchicine compared with placebo on high sensitivity C-reactive protein in patients with acute coronary syndrome or acute stroke: a pilot randomized controlled trial

Nina C. Raju, Qiang Yi, Mark Nisford, Nick D. Fogel, Rajesh Hiralal, John W. Ezekowitz

Published online: 15 September 2001
© Springer Science+Business Media, LLC 2001

Abstract There is a need for more effective therapies to reduce morbidity and mortality from cardiovascular disease. Inflammation plays a central role in the pathogenesis of atherosclerosis but no randomized studies have evaluated anti-inflammatory therapy in patients with acute coronary or cerebrovascular disease. We performed a pilot randomized controlled trial comparing the effect of colchicine 1 mg per day with placebo on high sensitivity C-reactive protein (CRP) levels and platelet function in 80 patients with acute coronary syndrome or acute ischemic stroke who were followed for 30 days. Clinical status was ascertained for 74 (92.5%) patients and CRP levels were obtained in 68 (85%) of patients at follow up. Colchicine

Electronic supplementary material The online version of this article (doi:10.1007/s10975-001-0067-7) contains supplementary material, which is available to authorized users.

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MHI EX

EX1028

Clinical Investigation

The Low Dose Colchicine after Myocardial Infarction (LoDoCo-MI) study: A pilot randomized placebo controlled trial of colchicine following acute myocardial infarction

Thomas Hawkey, Linda Sub, Mitchell Brown, Rachel Kuper, Carl Schibye, Sandra Patel, and Graham S. Hillis, University of Western Australia and Sydney and Faculty of Medicine, University of Sydney

Background Following an acute myocardial infarction (MI), patients with persistent inflammation, in particular C-reactive protein (CRP), are at a significantly increased risk of future cardiovascular events. Colchicine is a unique anti-inflammatory medication that has shown promise in reducing early coronary heart disease. The current study tested the ability of low dose colchicine to reduce CRP levels, a key marker of future outcome, and its safety and tolerability in this setting.

Methods We conducted a randomized, double-blind, trial of low-dose colchicine (0.5 mg 237 patients identified with an acute MI. The primary endpoint was the proportion of patients with CRP level ≥ 2.0 mg/L after 30 days of treatment, a threshold associated with a worse prognosis.

Results At 30-day follow-up, 44% of patients treated with colchicine had a CRP level ≥ 2.0 mg/L compared to 45% in the placebo group ($P = .35$) and the median CRP in patients randomized to colchicine was [IQR 0.7–2.5] compared to 2.0 mg/L [IQR 0.7–4.0] in patients randomized to placebo (P -reduction in CRP levels was -4.3 mg/L [-1.1 to -14.1] among colchicine treated patients, -14.4 , $P = .44$) in placebo treated patients. The relative reduction was a full of 78% compared to dose colchicine was well tolerated and did not reduce compliance with other secondary prevention.

Conclusion Treatment with low dose colchicine was safe and well tolerated, but was not of increased likelihood of achieving a CRP level < 2 mg/L or lower absolute levels of CRP 30 days (2019,215-62/9).

Inflammation is central to the pathogenesis of atherosclerosis and is a key mediator of cardiovascular disease. Colchicine, a unique anti-inflammatory medication, has shown promise in reducing early coronary heart disease. The current study tested the ability of low dose colchicine to reduce CRP levels, a key marker of future outcome, and its safety and tolerability in this setting.

One such approach is to target specific pro-inflammatory cytokines. This strategy was recently tested in the Colchicine & Anti-Inflammation Therapy in Myocardial Infarction (CANTIM) study.

In conclusion, we found no significant reduction in the median level of CRP, the absolute or relative reduction in levels or the percentage of patients who had levels of CRP below 2 mg/L after 30-days. All were, however, lower in colchicine treated patients which is consistent with prior data. We believe, therefore, that the totality of evidence supports the need for a large scale outcome trial in patients with recent MI. Importantly in this regard the current study demonstrates the safety and tolerability of low dose colchicine after acute MI.

EX2055

Archives of Cardiovascular Disease 2017;110, 395–402

Available online at ScienceDirect
www.sciencedirect.com
Elsevier Masson France
EMconsulte
www.em-consulte.com/en

CLINICAL RESEARCH

COLIN trial: Value of colchicine in the treatment of patients with acute myocardial infarction and inflammatory response

In our study, the effect of colchicine in the context of STEMI could not be demonstrated, with no improvement in inflammatory profiles or diminution of infarct size. Further larger studies with an appropriate population may be beneficial to clarify the impact of colchicine in STEMI patients.

KEYWORDS
Colchicine
Cardiovascular disease

Summary
Background – Inflammation is involved during acute myocardial infarction, and could be an interesting target to prevent ischemia-reperfusion injury. Colchicine, known for its pleiotropic anti-inflammatory effects, could decrease systemic inflammation in this context.

Abbreviations: AMI, Acute myocardial infarction; CRP, C-reactive protein; hs-CRP, High sensitivity cardiac troponin T; LAD, Left anterior descending artery; MACE, Major adverse cardiovascular events; P2Y12, P2Y12 receptor antagonist; STEMI, ST-segment elevation myocardial infarction.

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https://doi.org/10.1016/j.acvd.2016.10.004

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MHI EXHIBIT 2055

U.S. Patent No. 11,400,063 (“the ‘063 Patent”)

‘063 Patent

(12) United States Patent
Tardif

(54) EARLY ADMINISTRATION OF LOW-DOSE COLCHICINE AFTER MYOCARDIAL INFARCTION

(71) Applicant: INSTITUT DE CARDIOLOGIE MONTREAL, Montreal (CA)

(72) Inventor: Jean-Claude Tardif, Montreal (CA)

(73) Assignee: INSTITUT DE CARDIOLOGIE DE MONTREAL, Montreal (CA)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: 17/097,285

(22) Filed: Nov. 13, 2020

(65) Prior Publication Data
US 2021/0145773 A1 May 20, 2021

Related U.S. Application Data

(60) Provisional application No. 63/093,988, filed on Oct. 20, 2020, provisional application No. 62/935,865, filed on Nov. 15, 2019.

(51) Int. Cl. A61K 31/365 (2006.01)

A61P 9/10 (2006.01)

(52) U.S. Cl. CPC A61K 31/365 (2013.01); A61P 9/10 (2018.01)

(58) Field of Classification Search CPC A61K 31/365

See application file for complete search history.

(56) References Cited

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10,265,281 B2 4/2019 Nidorf

FOREIGN PATENT DOCUMENTS

WO WO-2014/066944 A1 5/2014

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(12) United States Patent
Tardif

(10) Patent No.: US 11,400,063 B2
(45) Date of Patent: Aug. 2, 2022

(54) EARLY ADMINISTRATION OF LOW-DOSE COLCHICINE AFTER MYOCARDIAL INFARCTION

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(72) Inventor: Jean-Claude Tardif, Montreal (CA)

(73) Assignee: INSTITUT DE CARDIOLOGIE DE MONTREAL, Montreal (CA)

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(65) Prior Publication Data
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Related U.S. Application Data

(60) Provisional application No. 63/093,988, filed on Oct. 20, 2020, provisional application No. 62/935,865, filed on Nov. 15, 2019.

MURRAY & POOLE EXHIBIT 1001

'063 Patent Independent "within about 3 days" Method Claims

'063 Patent

 US011400063B2	
(12) United States Patent Tardif	(10) Patent No.: US 11,400,063 B2 (45) Date of Patent: Aug. 2, 2022
(54) EARLY ADMINISTRATION OF LOW-DOSE COLCHICINE AFTER MYOCARDIAL INFARCTION	OTHER PUBLICATIONS Modet et al., "Impact of colchicine in the treatment of acute myocardial infarction: results from the heart failure in a mouse model," <i>Int J Cardiol</i> 240:347-353 (2017). Boushahkasi et al., "Time-to-onset initiation of colchicine and cardiovascular outcomes after myocardial infarction in the Colchicine Cardiovascular Outcomes Trial (COLCOT)," <i>Tex Heart J</i> 90:1-8 (2020). Defensor et al., "Anti-Inflammatory Treatment with Colchicine in Acute Myocardial Infarction: A Pilot Study," <i>Circulation</i> 132(15):1395-403 (2015). Hemmeny et al., "The Low Dose Colchicine after Myocardial Infarction (LoDoCa-MI) study: A pilot randomized placebo controlled trial of colchicine following acute myocardial infarction," <i>Ann Heart J</i> 21(5):62-69 (2019). Newby et al., "Inflammation as a Treatment Target after Acute Myocardial Infarction," <i>N Engl J Med</i> 381(26):2495-2505 (2019). Nidorf et al., "Low-dose colchicine for secondary prevention of cardiovascular disease," <i>J Am Coll Cardiol</i> 61:1410-1419 (2013). Nidorf et al., "Why Colchicine Should Be Considered for Secondary Prevention of Atherosclerosis: An Overview," <i>Clin Ther</i> 41(1):41-46 (2019). Tardif et al., "Efficacy and Safety of Low-Dose Colchicine after Myocardial Infarction," <i>N Engl J Med</i> 381(26):2495-2505 (2019). Tucker et al., "Colchicine as a Novel Therapy for Suppressing Chemokine Production in Patients with an Acute Coronary Syndrome: A Pilot Study," <i>Clin Ther</i> 41(10):2172-2181 (2019). Vaidya et al., "Colchicine Therapy and Plaque Stabilization in Patients with Acute Coronary Syndrome: ACT Coronary Angiography Study," <i>JACC: Cardiovasc Imaging</i> 11(12 Pt 2):305-316 (2018). Vaidya et al., "The Role of Colchicine in Acute Coronary Syndrome," <i>Clin Ther</i> 41(1):11-20 (2018). Office Action for Canadian Patent Application No. 3,099,143 dated Mar. 5, 2021 (9 pages). Montreal Heart Institute, "Colchicine Cardiovascular Outcomes Trial (COLCOT) (COLCOT)," U.S. National Library of Medicine, NCT02551094, dated Sep. 16, 2015 (9 pages). Office Action for Canadian Patent Application No. 3,099,143 dated Sep. 16, 2021 (4 pages).
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(72) Inventor: Jean-Claude Tardif, Montreal (CA)	
(73) Assignee: INSTITUT DE CARDIOLOGIE DE MONTREAL, Montreal (CA)	
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(51) Int. Cl. A61K 31/365 (2006.01) A61P 9/10 (2006.01)	
(52) U.S. Cl. CPC A61K 31/365 (2013.01); A61P 9/10 (2013.01)	
(58) Field of Classification Search CPC A61K 31/365 See application file for complete search history.	Primary Examiner —Brian J Davis (74) Attorney, Agent, or Firm —Clark & Elbing LLP
(56) References Cited U.S. PATENT DOCUMENTS 10,265,281 B2 4/2019 Nidorf FOREIGN PATENT DOCUMENTS WO WO-2014/066944 A1 5/2014	ABSTRACT (57) The invention relates to colchicine for use in a method of treating a patient after having a myocardial infarction (MI), the method including initiating the administration of colchicine at a daily low dose to the patient within about 3 days of the MI. 50 Claims, 3 Drawing Sheets

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MURRAY & POOLE EXHIBIT 1001

1. A method of treating a patient after having a myocardial infarction (MI), the method comprising initiating the administration of colchicine at a daily low dose to the patient within about 3 days of the MI, wherein the colchicine is administered without pre-loading the patient with a higher dose of colchicine before the administration at the daily low dose, wherein percutaneous coronary intervention was performed for treating the patient's MI.

8. A method of treating a patient after having a myocardial infarction (MI), the method comprising initiating the administration of colchicine at a daily low dose to the patient within about 3 days of the MI, wherein the colchicine is administered without pre-loading the patient with a higher dose of colchicine before the administration at the daily low dose, wherein the patient is at a lower risk of a cardiovascular event, relative to a patient not being administered colchicine, and wherein the cardiovascular event is resuscitated cardiac arrest, stroke, or urgent hospitalization for angina requiring coronary revascularization.

'063 Patent Independent "reducing risk of stroke" Method Claim

'063 Patent

(32) United States Patent Tardif

(10) Patent No.: US 11,400,063 B2
(45) Date of Patent: Aug. 2, 2022



(54) EARLY ADMINISTRATION OF LOW-DOSE COLCHICINE AFTER MYOCARDIAL INFARCTION
(71) Applicant: INSTITUT DE CARDIOLOGIE DE MONTREAL, Montreal (CA)
(72) Inventor: Jean-Claude Tardif, Montreal (CA)
(73) Assignee: INSTITUT DE CARDIOLOGIE DE MONTREAL, Montreal (CA)
(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: 17/097,285
(22) Filed: Nov. 13, 2020
(65) Prior Publication Data
US 2021/0145773 A1 May 20, 2021

Related U.S. Application Data
(60) Provisional application No. 63/093,988, filed on Oct. 20, 2020, provisional application No. 62/935,865, filed on Nov. 15, 2019.

(51) Int. Cl. A61K 31/365 (2006.01)
A61P 9/10 (2006.01)
(52) U.S. Cl. CPC A61K 31/365 (2013.01); A61P 9/10 (2018.01)

(56) Field of Classification Search
CPC A61K 31/365
See application file for complete search history.

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U.S. PATENT DOCUMENTS
10,265,281 B2 4/2019 Nidorf
FOREIGN PATENT DOCUMENTS
WO WO/2014/066944 A1 5/2014

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Defensor et al., "Anti-Inflammatory Treatment with Colchicine in Acute Myocardial Infarction: A Pilot Study," *Circulation* 132(15):1395-403 (2015).
Hernandez et al., "The Low Dose Colchicine after Myocardial Infarction (LoDoCaMI) study: A pilot randomized placebo controlled trial of colchicine following acute myocardial infarction," *Am Heart J* 215(62-69) (2019).
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Nidorf et al., "Low-dose colchicine for secondary prevention of cardiovascular disease," *J Am Coll Cardiol* 61(14):1406-1410 (2013).
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Tardif et al., "Colchicine as a Novel Therapy for Suppressing Chemokine Production in Patients with an Acute Coronary Syndrome: A Pilot Study," *Clin Ther* 41(10):2172-2181 (2019).
Vaidya et al., "Colchicine Therapy and Plaque Stabilization in Patients with Acute Coronary Syndrome: ACT Coronary Angiography Study," *JACC Cardiovasc Imaging* 11(12 Pt 2):305-316 (2018).
Vaidya et al., "The Role of Colchicine in Acute Coronary Syndrome," *Clin Ther* 41(1):11-20 (2018).
Office Action for Canadian Patent Application No. 3,099,143 dated Mar. 5, 2021 (9 pages).
Montreal Heart Institute, "Colchicine Cardiovascular Outcomes Trial (COLCOT) (COLCOT); U.S. National Library of Medicine, NCT02551094, dated Sep. 16, 2015 (9 pages).
Office Action for Canadian Patent Application No. 3,099,143 dated Sep. 16, 2021 (4 pages).

Primary Examiner—Brian J Davis
(74) Attorney, Agent, or Firm—Clark & Elbing LLP

(57) ABSTRACT
The invention relates to colchicine for use in a method of treating a patient after having a myocardial infarction (MI), the method including initiating the administration of colchicine at a daily low dose to the patient within about 3 days of the MI.

50 Claims, 3 Drawing Sheets

27. A method of reducing the risk of a stroke in a patient after having an MI, the method comprising initiating the administration of colchicine at a daily low dose to the patient within about 30 days of an MI.

Claim Construction

Applicable Law: Preamble “life, meaning, and vitality”



“[I]f the claim preamble is “necessary to give life, meaning, and vitality” to the claim, then the claim preamble should be construed as if in the balance of the claim.”

Pitney Bowes, Inc. v. Hewlett-Packard Co., 182 F.3d 1298, 1305 (Fed. Cir. 1999).



“[A]s it frequently does for method claims: [preambles] are not merely circumstances in which the method may be useful, but instead are the *raison d’être* of the claimed method itself.”

Boehringer Ingelheim Vetmedica, Inc. V. Schering-Plough Corp.,
320 F.3d 1339, 1345 (Fed. Cir. 2003).

Applicable Law: Preamble Antecedent Basis and Distinguishing



“When limitations in the body of the claim rely upon and derive antecedent basis from the preamble, then the preamble may act as a necessary component of the claimed invention.”

Eaton Corp. v. Rockwell Intern. Corp., 323 F.3d 1332, 1339 (Fed. Cir. 2003).



“[C]lear reliance on the preamble during prosecution to distinguish the claimed invention from the prior art transforms the preamble into a claim limitation because such reliance indicates use of the preamble to define, in part, the claimed invention.”

Invitrogen Corp. v. Biocrest Mfg., L.P., 327 F.3d 1364, 1370 (Fed. Cir. 2013) (citations omitted)

“reducing the risk of a stroke in a patient after having an MI”

27. A method of reducing the risk of a stroke in a patient after having an MI, the method comprising initiating the administration of colchicine at a daily low dose to the patient within about 30 days of an MI.

- Applies to claims 27-39.
- Result of the COLCOT clinical trial showed reduction in the risk of stroke in post-MI patients.
- The reason to administer low dose colchicine within about 30 days of an MI is to reduce the risk of stroke in a patient after having an MI.

Specification Supports Limiting Stroke Reduction Preamble

TABLE 3

Efficacy endpoints according to TTI (N = 4661, colchicine vs. placebo)			
Endpoints	TTI 0-3 days, N = 1193 Colchicine vs. placebo no. (%) HR (95% CI); p	TTI 4-7 days, N = 720 Colchicine vs. placebo no. (%) HR (95% CI); p	TTI ≥ 8 days, N = 2748 Colchicine vs. placebo no. (%) HR (95% CI); p
Primary composite endpoint	26 (4.3%) vs. 49 (8.3%) 0.52 (0.32-0.84); p = 0.007	22 (6.0%) vs. 21 (5.9%) 0.96 (0.53-1.75); p = 0.896	77 (5.7%) vs. 99 (7.1%) 0.82 (0.61-1.11); p = 0.200
CV death	2 (0.3%) vs. 2 (0.3%) 1.04 (0.15-7.37); p = 0.970	2 (0.5%) vs. 4 (1.1%) 0.45 (0.08-2.46); p = 0.356	15 (1.1%) vs. 18 (1.3%) 0.89 (0.45-1.76); p = 0.734
Resuscitated cardiac arrest	1 (0.2%) vs. 3 (0.5%) 0.33 (0.03-3.20); p = 0.340	2 (0.5%) vs. 1 (0.3%) 1.90 (0.17-20.95); p = 0.600	2 (0.1%) vs. 2 (0.1%) 1.02 (0.14-7.22); p = 0.986
MI	17 (2.8%) vs. 29 (4.9%) 0.58 (0.32-1.05); p = 0.071	16 (4.4%) vs. 9 (2.5%) 1.67 (0.74-3.78); p = 0.218	52 (3.8%) vs. 59 (4.2%) 0.93 (0.64-1.35); p = 0.710
Stroke	1 (0.2%) vs. 5 (0.8%) 0.21 (0.02-1.81); p = 0.156	1 (0.3%) vs. 3 (0.8%) 0.28 (0.03-2.71); p = 0.272	2 (0.1%) vs. 11 (0.8%) 0.19 (0.04-0.84); p = 0.029

TABLE 13

Major Clinical End-points (Intention-to-Treat Population)				
End Point	Colchicine (N = 2366)	Placebo (N = 2379)	Hazard Ratio (95% CI)	P Value
	number (percent)			
Primary composite end point	131 (5.5)	170 (7.1)	0.77 (0.61-0.96)	0.02†
Components of primary end point				
Death from cardiovascular causes	20 (0.8)	24 (1.0)	0.84 (0.46-1.52)	
Resuscitated cardiac arrest	5 (0.2)	6 (0.3)	0.83 (0.25-2.73)	
Myocardial infarction	89 (3.8)	98 (4.1)	0.91 (0.68-1.21)	
Stroke	5 (0.2)	19 (0.8)	0.26 (0.10-0.70)	
Urgent hospitalization for angina leading to revascularization	25 (1.1)	50 (2.1)	0.50 (0.31-.0.81)	
Secondary composite end point†	111 (4.7)	130 (5.5)	0.85 (0.66-1.10)	
Death	43 (1.8)	44 (1.8)	0.98 (0.64-1.49)	
Deep venous thrombosis or pulmonary embolus	10 (0.4)	7 (0.3)	1.43 (0.54-3.75)	
Atrial fibrillation	36 (1.5)	40 (1.7)	0.93 (0.59-1.46)	

Specification Supports Limiting Stroke Reduction Preamble

those who received placebo. Patients receiving low dose
15 colchicine had reduced morbidity relative to placebo, as is
demonstrated by the rates of the respective primary composite end points for the two patient populations ($P=0.02$).
This reduction in morbidity was particularly prominent
among colchicine-receiving patients in the reduction of
20 severe conditions, such as stroke and urgent hospitalization
for angina leading to revascularization: hazard ratios are
0.26 (95% confidence interval is 0.10-0.70) and 0.50 (95%
confidence interval is 0.31-0.81), respectively. Still further,
unlike the use of the anti-inflammatory canakinumab for
25 atherosclerotic events, colchicine did not increase the incidence of septic shock. Moreover, no serious adverse event of myopathy linked to colchicine occurred despite the use of statins in 99% of trial participants.

Prosecution History Supports Limiting Stroke Reduction Preamble

With respect to claims 29-31, the closest prior art also appears to be *American Heart Journal* (September 2019), Vol. 215, pp. 62-69, outlined above. The reference does not teach, show, suggest or make obvious the instant **method of reducing the risk of a stroke** in a patient having had a myocardial infarction by the administration of daily low dose colchicine within about 30 days of the myocardial infarction.

EX1002 at 399 – Notice of Allowance.

Petitioner's Inapposite Case Law

- *Bristol-Myers Squibb Co. v. Ben Venue Labs., Inc.*, 246 F.3d 1368, 1375 (Fed. Cir. 2001)
 - Did not involve method “new use distinguishes the process over the prior art”
 - Manipulative difference is not the standard
- *IMS Tech., Inc. v. Haas Automation, Inc.*, 206 F.3d 1422, 1434 (Fed. Cir. 2000)
- *Rowe v. Dror*, 112 F.3d 472, 478 (Fed. Cir. 1997)
 - Both involve apparatus claims in fields very different from method of medical treatments.

Applicable Law: “Wherein” Clauses are Material Limitations



“When a ‘whereby’ or ‘wherein’ clause states a condition that is material to patentability, it cannot be ignored in order to change the substance of the invention.”

Allergan Sales, LLC v. Sandoz, Inc., 935 F.3d 1370, 1376 (Fed. Cir. 2019) (quoting *Hoffer v. Microsoft Corp.*, 405 F.3d 1326, 1329 (Fed. Cir. 2005)).

The “wherein” Claim Limitations – Claims 8-11, 20-23, 40-50

8. A method of treating a patient after having a myocardial infarction (MI), the method comprising initiating the administration of colchicine at a daily low dose to the patient within about 3 days of the MI, wherein the colchicine is administered without pre-loading the patient with a higher dose of colchicine before the administration at the daily low dose, wherein the patient is at a lower risk of a cardiovascular event, relative to a patient not being administered colchicine, and wherein the cardiovascular event is resuscitated cardiac arrest, stroke, or urgent hospitalization for angina requiring coronary revascularization.

The “wherein” of ‘063 and *Allergan* Patent

8. A method of treating a patient after having a myocardial infarction (MI), the method comprising initiating the administration of colchicine at a daily low dose to the patient within about 3 days of the MI, wherein the colchicine is administered without pre-loading the patient with a higher dose of colchicine before the administration at the daily low dose, wherein the patient is at a lower risk of a cardiovascular event, relative to a patient not being administered colchicine, and wherein the cardiovascular event is resuscitated cardiac arrest, stroke, or urgent hospitalization for angina requiring coronary revascularization.



“A method of treating a patient with glaucoma or ocular hypertension comprising topically administering twice daily to an affected eye a single composition comprising 0.2% w/v brimonidine tartrate and 0.68% w/v timolol maleate, wherein the method is as effective as the administration of 0.2% w/v brimonidine tartrate monotherapy three times per day and wherein the method reduces the incidence of one or more adverse events selected from the group consisting of conjunctival hyperemia, oral dryness, eye pruritus, ...when compared to the administration of 0.2% w/v brimonidine tartrate monotherapy 3 times daily”

Allergan Sales, LLC v. Sandoz, Inc., 935 F.3d 1370 (Fed. Cir. 2019)

“Wherein” Clauses Material to Patentability

Examiner allowed claims when “wherein” clauses were added:

In particular, the reference does not teach show suggest or make obvious the cardiovascular events: resuscitated cardiac arrest, stroke, or urgent hospitalization for angina requiring coronary revascularization.

EX1002 at 398-99, Notice of Allowance

“Wherein” Clauses Provide Antecedent Basis

8. A method of treating a patient alter having a myocardial infarction (MI), the method comprising initiating the administration of colchicine at a daily low dose to the patient within about 3 days of the MI, wherein the colchicine is administered without pre-loading the patient with a higher dose of colchicine before the administration at the daily low dose, wherein the patient is at a lower risk of a cardiovascular event, relative to a patient not being administered colchicine, and wherein the cardiovascular event is resuscitated cardiac arrest, stroke, or urgent hospitalization for angina requiring coronary revascularization.

Ground 1: No Anticipation Based on Bouabdallaoui

Bouabdallaoui (EX1005) Is NOT Prior Art

- EX1005 was published AFTER priority date.
- Petitioner has provided no evidence that Dr. Bouabdallaoui, or anyone other than Dr. Tardif, is an inventor. Only conjecture.
- No argument that Dr. Tardif solely conceived the COLCOT study, which EX1005 describes, summarizes, and analyzes.
- No argument that Dr. Tardif is the corresponding author for the EX1005.
- Dr. Tardif made disclosures in EX1005 within 1-year grace period for latest possible priority date.

EX1005 Published AFTER Priority Date

'063 Patent



(12) **United States Patent**
Tardif
(10) Patent No.: **US 11,400,063 B2**
(45) Date of Patent: **Aug. 2, 2022**

(54) **EARLY ADMINISTRATION OF LOW-DOSE COLCHICINE AFTER MYOCARDIAL INFARCTION**
(71) OTHER PUBLICATIONS
Abdel et al., "Interest of colchicine in the treatment of acute myocardial infarction: a meta-analysis of randomized controlled trials," *Journal of Card Pharmacology*, vol. 58, no. 1, pp. 1-10, 2016.

Related U.S. Application Data

(60) Provisional application No. 63/093,988, filed on Oct. 20, 2020, provisional application No. 62/935,865, filed on Nov. 15, 2019.

(60) Provisional application No. 63/093,988, filed on Oct. 20, 2020, provisional application No. 62/935,865, filed on Nov. 15, 2019.
(51) Int. Cl. **A61K 31/365** (2006.01)
A61P 9/10 (2006.01)
(52) U.S. Cl. **A61K 31/365** (2013.01); **A61P 9/10** (2018.01)
(58) **Field of Classification Search**
CPC **A61K 31/365**
See application file for complete search history.
(56) **References Cited**
U.S. PATENT DOCUMENTS
10,205,281 B2 4/2019 Nidef
FOREIGN PATENT DOCUMENTS
WO WO/2014/069944 A1 5/2014
50 Claims, 3 Drawing Sheets

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MURRAY & POOLE EXHIBIT 1001

EX1005



European Heart Journal (2020) 41, 4092–4099
doi:10.1093/eurheartj/ehaa659

FAST TRACK CONGRESS

Intensive cardiac care and acute coronary syndromes

Time-to-treatment initiation of colchicine and cardiovascular outcomes after myocardial infarction in the Colchicine Cardiovascular Outcomes Trial (COLCOT)

Nadia Bouabdallaoui¹, Jean-Claude Tardif^{1*}, David D. Waters², Fausto J. Pinto³, Aldo P. Maggioni⁴, Rafael Diaz⁵, Colin Berry⁶, Wolfgang Koenig^{7,8,9}, Jose Lopez-Sendon¹⁰, Habib Gamra¹¹, Ghassan S. Kiwan¹², Lucie Blondeau¹³, Andreas Orfanos¹³, Reda Ibrahim¹, Jean C. Grégoire¹, Marie-Pierre Dubé¹, Michelle Samuel¹, Olivier Morel^{1,4,15}, Pascal Lim¹⁶, Olivier F. Bertrand¹⁷, Simon Kouz¹⁸, Marie-Claude Guertin¹³, Philippe L. L'Allier¹, and Francois Roubille¹⁹

¹Montreal Heart Institute, 5000 Belanger Street, Montreal, Quebec H3T 1C8, Canada and Université de Montréal, Montreal, Quebec, Canada; ²San Francisco General Hospital, California; ³Santa Maria University Hospital (CHULN), CML, CCL, Faculdade de Medicina de Universidade de Lisboa, Lisboa, Portugal; ⁴ANMCO Research Center, Firenze, Italy; ⁵Cardiovascular Laboratory, Hospital de Braga, Braga, Portugal; ⁶Cardiovascular Research Institute, University of Toronto, Toronto, Canada; ⁷University of Cologne, Cologne, Germany; ⁸University of Cologne, Cologne, Germany; ⁹University of Cologne, Cologne, Germany; ¹⁰University of Seville, Seville, Spain; ¹¹University of Seville, Seville, Spain; ¹²University of Seville, Seville, Spain; ¹³University of Seville, Seville, Spain; ¹⁴University of Seville, Seville, Spain; ¹⁵University of Seville, Seville, Spain; ¹⁶University of Seville, Seville, Spain; ¹⁷University of Seville, Seville, Spain; ¹⁸University of Seville, Seville, Spain; ¹⁹University of Seville, Seville, Spain.

online publish-ahead-of-print 29 August 2020

after myocardial infarction (MI). We aimed to determine whether time-to-treatment initiation (TTI) influences the beneficial impact of colchicine.
Methods and results
In COLCOT, patients were randomly assigned to receive colchicine or placebo within 30 days post-MI. Time-to-treatment initiation was defined as the length of time between the index MI and the initiation of study medication. The primary efficacy endpoint was a composite of cardiovascular death, resuscitated cardiac arrest, MI, stroke, or urgent hospitalization for angina requiring coronary revascularization. The relationship between endpoints and various TTI (<3, 4–7 and >8 days) was examined using multivariable Cox regression models. Amongst the 4661 patients included in this analysis, there were 1193, 720, and 2748 patients, respectively, in the three TTI strata. After a median follow-up of 22.7 months, there was a significant reduction in the incidence of the primary endpoint for patients in whom colchicine was initiated < Day 3 compared with placebo [hazard ratios (HR) = 0.52, 95% confidence intervals (CI) 0.32–0.84], in contrast to patients in whom colchicine was initiated between Days 4 and 7 (HR = 0.96, 95% CI 0.53–1.75) or > Day 8 (HR = 0.82, 95% CI 0.61–1.11). The beneficial effects of early initiation of colchicine were also demonstrated for urgent hospitalization for angina requiring revascularization (HR = 0.35).

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MURRAY & POOLE EXHIBIT 1005

'865 Provisional Application Disclosed Time to Initiate Limitations

'063 Patent

(12) United States Patent
Tardif

(10) Patent No.: US 11,400,063 B2
(45) Date of Patent: Aug. 2, 2022

1. A method of treating a patient after having a myocardial infarction (MI), the method comprising initiating the administration of colchicine at a daily low dose to the patient **within about 3 days of the MI** wherein the colchicine is administered without pre-loading the patient with a higher dose of colchicine before the administration at the daily low dose, wherein percutaneous coronary intervention was performed for treating the patient's MI.

Related U.S. Application Data

(60) Provisional application No. 63/093,988, filed on Oct. 20, 2020; provisional application No. 62/935,865, filed on Nov. 15, 2019.

(51) Int. Cl.
A61K 31/365 (2006.01)
A61P 9/10 (2006.01)

(52) U.S. Cl.
CPC A61K 31/365 (2013.01); A61P 9/10

Vaidya et al., "Colchicine Therapy and Plaque Stabilization in Patients with Acute Coronary Syndrome: ACT Coronary Angiography Study," *JACC Cardiovasc Imaging*, 11(2 Pt 2):305-316 (2018).
Vaidya et al., "The Role of Colchicine in Acute Coronary Syndromes," *Clin Ther*, 41(11):11-20 (2018).
Office Action for Canadian Patent Application No. 3,089,143 dated Mar. 5, 2021 (6 pages).
Montreal Heart Institute, "Colchicine Cardiovascular Outcomes Trial (COLCOT) (COLECO)"; U.S. National Library of Medicine, NCT02551094, dated Sep. 16, 2015 (9 pages).
Office Action for Canadian Patent Application No. 3,089,143 dated

28. The method according to claim 27, wherein the method comprises administering colchicine **within 4 to 7 days of the MI**.

EX1004

PATENT
ATTORNEY DOCKET NO. 50761-022001

METHODS FOR USING LOW-DOSE COLCHICINE AFTER MYOCARDIAL INFARCTION

Background of the Invention

5

The invention relates to a treatment regimen for patients after suffering a myocardial infarction.

Inflammation appears to play an important role in atherosclerosis (Hansson GK, Inflammation, atherosclerosis, and coronary artery disease. *N Engl J Med* 2005;352:1685-95). Inhibition of interleukin-1 β by the injectable monoclonal antibody canakinumab led to a 15% lower risk of cardiovascular events than was observed with placebo in the Canakinumab Antiinflammatory Thrombosis Outcomes Study (CANTOS) but also led to a slightly higher incidence of fatal infections (Ridker PM et al., Antiinflammatory therapy with canakinumab for atherosclerotic disease. *N Engl J Med* 2017;377:1119-31). In contrast, methotrexate did not affect cardiovascular outcomes or plasma markers of inflammation in the Cardiovascular Inflammation Reduction Trial (CIRT) (Ridker PM et al., Low-dose methotrexate for the prevention of atherosclerotic events. *N Engl J Med* 2019;380:752-62). Considering these differing results and given that canakinumab is not clinically available for cardiovascular prevention, the search for a

In some embodiments, the method involves **administering colchicine within 5, 10, 15, 20, or 25 days of the MI**. In some embodiments, the method includes administering colchicine **within 10 days of the myocardial infarction**. In still other embodiments, the method includes administering colchicine within 15 days of the myocardial infarction. In yet other embodiments, the method includes administering colchicine at about 30 days of the myocardial infarction (for example, at 31, 32, or 33 days).

therapy for acute pericarditis: results of the COchicine for acute PEricarditis (COPE) trial. *Circulation* 2005;112:2012-6).

35

In the Low-Dose Colchicine (LoDoCo) trial, patients with stable coronary disease treated with colchicine at a dose of 0.5 mg once daily had fewer cardiovascular events than those not receiving colchicine (Nidorf SM et al., Low-dose colchicine for secondary prevention of cardiovascular disease. *J Am Coll*

'865 Provisional Application CLAIMED Time to Initiate Limitations

'063 Patent

(12) United States Patent
Tardif

(10) Patent No.: US 11,400,063 B2
(45) Date of Patent: Aug. 2, 2022

1. A method of treating a patient after having a myocardial infarction (MI), the method comprising initiating the administration of colchicine at a daily low dose to the patient within about 3 days of the MI wherein the colchicine is administered without pre-loading the patient with a higher dose of colchicine before the administration at the daily low dose, wherein percutaneous coronary intervention was performed for treating the patient's MI.

Related U.S. Application Data

(60) Provisional application No. 63/093,588, filed on Oct. 20, 2020; provisional application No. 62/935,865, filed on Nov. 15, 2019.

(51) Int. Cl.

A61K 31/365

(2006.01)

A61P 9/10

(2006.01)

(52) U.S. Cl.

CPC

A61K 31/365 (2013.01); A61P 9/10

Vaidya et al., "Colchicine Therapy and Plaque Stabilization in Patients with Acute Coronary Syndrome: ACT Coronary Angiography Study," *JACC Cardiovasc Imaging*, 11 (2 Pt 2):305-316 (2018).

Vaidya et al., "The Role of Colchicine in Acute Coronary Syndromes," *Clin Ther*, 41 (1): 11-20 (2018).

Office Action for Canadian Patent Application No. 3,099,143 dated Mar. 5, 2021 (6 pages).

Montreal Heart Institute, "Colchicine Cardiovascular Outcomes Trial (COLCOT) (NCT02551094)," U.S. National Library of Medicine, NCT02551094, dated Sep. 16, 2015 (9 pages).

Office Action for Canadian Patent Application No. 3,099,143 dated

28. The method according to claim 27, wherein the method comprises administering colchicine within 4 to 7 days of the MI.

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MURRAY & POOLE EXHIBIT 1001

EX2067

PATENT
ATTORNEY DOCKET NO. 50761-022001

CLAIMS

1. Colchicine for use in a method of treating a patient after having a myocardial infarction (MI), the method comprising initiating the administration of colchicine at a daily low dose to the patient within about 30 days of the MI.
2. Colchicine for use according to claim 1, wherein the method comprises administering colchicine within 5, 10, 15, 20, or 25 days of the MI.
3. Colchicine for use according to claim 2, wherein the method comprises administering colchicine within 10 days of the MI.

ischemic cardiovascular event.

11. Colchicine for use according to any one of claims 1-10, wherein the administration of colchicine is initiated upon assessment in (a) an emergency department (ED), (b) the hospital, or (c) a medical office setting.

12. Colchicine for use according to any one of claims 1-11, wherein the colchicine is in the form of a tablet.

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Page 1 of 2

MHI EXHIBIT 2067

Evidence Corroborates Nov. 15, 2019 Priority

EX2071



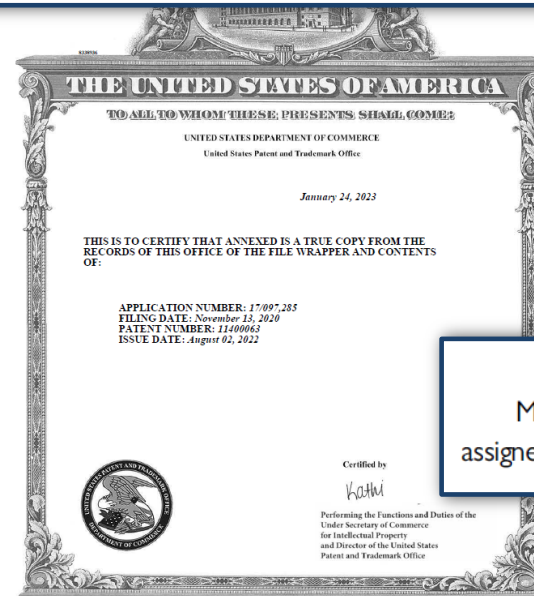
Bouabdallaoui et al., "Time-to-treatment initiation of colchicine and cardiovascular outcomes after myocardial infarction in the Colchicine Cardiovascular Outcomes Trial (COLCOT)," Eur Heart J. 00:1-8 (2020).

I guess my question is simply, in your opinion, does -- does the regimen of initiating treatment within about three days of the MI overlap with initiating treatment within five days of the MI?

A And what I think I've said multiple times now is that what this is really all about is when the patient is stable, and when we decide as responsible physicians to put patients on the long-term therapies that we know they need to prevent second heart attacks, second strokes down the road. And that might occur for some patients at day two or three. Other patients, it might occur at day five.

It's just about -- it's -- it's this issue that you raised earlier. It's when they're stable is when we initiate these treatments.

EX1002



Page 1 of 438

MURRAY & POOLE EXHIBIT 1002

EX1005



European Heart Journal (2020) 41, 4092–4099
Intensive cardiac care and acute coronary syndromes

FAST TRACK CONGRESS

Time-to-treatment initiation of colchicine and cardiovascular outcomes after myocardial infarction in the Colchicine Cardiovascular Outcomes Trial (COLCOT)

Nadia Bouabdallaoui¹, Jean-Claude Tardif^{1*}, David D. Waters², Fausto J. Pinto³, Aldo P. Maggioni⁴, Rafael Diaz⁵, Colin Berry⁶, Wolfgang Koenig^{7,8,9}, Jose Lopez-Sendon¹⁰, Habib Gamra¹¹, Ghassan S. Kiwan¹², Lucie Blondeau¹³, Andreas Orfanos¹³, Reda Ibrahim¹, Jean C. Gregoire¹, Marie-Pierre Dubé¹, Michelle Samuel¹, Olivier Moret^{14,15}, Pascal Lim¹⁶, Olivier F. Bertrand¹⁷, Simon Kouz¹⁸, Marie-Claude Guertin¹³, Philippe L. L'Allier¹, and Francois Roubille¹⁹

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Received 1 July 2020; revised 15 July 2020; accepted 27 July 2020; accepted 28 July 2020; online publication 29 August 2020
See page 4100 for the editorial comment on this article (doi:10.1093/eurheartj/ehaa752)

Methods for using low-dose colchicine after MI pending to Invention assigned to the Montreal Heart Institute,

of colchicine were also demonstrated for urgent hospitalization for angina requiring revascularization (HR=0.35).

* Corresponding author: jean-claude.tardif@umontreal.ca

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MURRAY & POOLE EXHIBIT 1005

EX1005 Published Within 1-Year of Latest Possible Priority

'063 Patent

(12) **United States Patent**
Tardif

(10) Patent No.: **US 11,400,063 B2**
(45) Date of Patent: **Aug. 2, 2022**

(54) **EARLY ADMINISTRATION OF LOW-DOSE COLCHICINE AFTER MYOCARDIAL INFARCTION**

(71) Applicant: **INSTITUT DE CARDIOLOGIE DE MONTREAL, Montreal (CA)**

(72) Inventor: **Jean-Claude Tardif, Montreal (CA)**

(51) Int. Cl. **A61K 31/365** (2006.01)
A61P 9/10 (2006.01)

(52) U.S. Cl. **A61K 31/365** (2013.01); **A61P 9/10** (2006.01)

(21) Appl. No.: **17/097,285**

(22) Filed: **Nov. 13, 2020**

Page 1 of 26

MURRAY & POOLE EXHIBIT 1001

EX1005

ESC European Heart Journal (2020) 41, 4092–4099
European Society of Cardiology doi:10.1093/eurheartj/ehaa559

FAST TRACK CONGRESS
Intensive cardiac care and acute coronary syndromes

Nadia Bouabdallaoui¹, **Jean-Claude Tardif^{1*}**, David D. Waters², Fausto J. Pinto³, Aldo P. Maggioni⁴, Rafael Diaz⁵, Colin Berry⁶, Wolfgang Koenig^{7,8,9}, Jose Lopez-Sendon¹⁰, Habib Gamra¹¹, Ghassan S. Kiwan¹², Lucie Blondeau¹³, Andreas Orfanos¹³, Reda Ibrahim¹, Jean C. Grégoire¹, Marie-Pierre Dubé¹, Michelle Samuel¹, Olivier Morel^{14,15}, Pascal Lim¹⁶, Olivier F. Bertrand¹⁷, Simon Kouz¹⁸, Marie-Claude Guertin¹³, Philippe L. L'Allier¹, and Francois Roubille¹⁹

* Corresponding author. Email: jean-claude.tardif@icm-mhi.org

Aims The COLchicine Cardiovascular Outcomes Trial (COLCOT) demonstrated the benefits of targeting inflammation after myocardial infarction (MI). We aimed to determine whether time-to-treatment initiation (TTI) influences the beneficial impact of colchicine.

online publish-ahead-of-print **29 August 2020**

of colchicine were also demonstrated for urgent hospitalization for angina requiring revascularization (HR=0.35).

* Corresponding author: Email: jean-claude.tardif@icm-mhi.org
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MURRAY & POOLE EXHIBIT 1005

EX1005 NOT Prior Art Under AIA § 102(b)

(b) Exceptions.

(1) Disclosures made 1 year or less before the effective filing date of the claimed invention. A disclosure made 1 year or less before the effective filing date of a claimed invention shall not be prior art to the claimed invention under subsection (a)(1) if—

(A) the disclosure was made by the inventor or joint inventor or by another who obtained the subject matter disclosed directly or indirectly from the inventor or a joint inventor; or

(B) the subject matter disclosed had, before such disclosure, been publicly disclosed by the inventor or a joint inventor or another who obtained the subject matter disclosed directly or indirectly from the inventor or a joint inventor.

Independent Evidence Corroborates Disclosure by Dr. Tardif

EX1005

ESC European Heart Journal (2020) 41, 4092–4099
FAST TRACK CONGRESS
Intensive cardiac care and acute coronary syndromes

Time-to-treatment initiation of colchicine and cardiovascular outcomes after myocardial

* Corresponding author. Email: jean-claude.tardif@icm-mhi.org

Wolfgang Koenig^{7,8,9}, Jose Lopez-Sendon¹⁰, Habib Gamra¹¹, Ghassan S. Kiwan¹², Lucie Blondeau¹³, Andreas Orfanos¹³, Reda Ibrahim¹, Jean C. Grégoire¹, Marie-Pierre Dubé¹, Michelle Samuel¹, Olivier Morel^{14,15}, Pascal Lim¹⁶, Olivier F. Bertrand¹⁷, Simon Kouz¹⁸, Marie-Claude Guertin¹³, Philippe L. L'Allier¹, and Francois Roubille¹⁹

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Received 1 July 2020; revised 15 July 2020; accepted 27 July 2020; accepted 28 July 2020 online published online 29 August 2020
See page 4100 for the editorial comment on this article (doi:10.1093/eurheartj/ehaa752)

Aims The COLCOT Cardiovascular Outcomes Trial (COLCOT) demonstrated the benefits of targeting inflammation after myocardial infarction (MI). We aimed to determine whether time-to-treatment initiation (TTI) influences the beneficial impact of colchicine.

Methods and results In COLCOT, patients were randomly assigned to receive colchicine or placebo within 30 days post-MI. Time-to-treatment initiation was defined as the length of time between the index MI and the initiation of study medication. The primary efficacy endpoint was a composite of cardiovascular death, revascularized cardiac arrest, MI, stroke, or urgent hospitalization for angina requiring revascularization. The relationship between endpoints and various TTI (<3, 4–7, and >8 days) was examined using multivariable Cox regression models. Amongst the 4661 patients included in this analysis, there were 1193, 720, and 2748 patients, respectively, in the three TTI strata. After a median follow-up of 22.7 months, there was a significant reduction in the incidence of the primary endpoint for patients in whom colchicine was initiated < Day 3 compared with placebo [hazard ratios (HR) = 0.52, 95% confidence intervals (CI) 0.33–0.84], in contrast to patients in whom colchicine was initiated between Days 4 and 7 (HR = 0.96, 95% CI 0.53–1.73) or > Day 8 (HR = 0.82, 95% CI 0.61–1.11). The beneficial effects of early initiation of colchicine were also demonstrated for urgent hospitalization for angina requiring revascularization (HR = 0.35).

* Corresponding author. Email: jean-claude.tardif@icm-mhi.org
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MURRAY & POOLE EXHIBIT 1005

EX1006

https://clinicaltrials.gov/ct2/show/NCT02551094 April 11, 2023 at 10:26 AM EDT
CT02551094

<https://clinicaltrials.gov/ct2/show/NCT02551094>

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Locations

Canada, Quebec

Montreal Heart Institute

Recruiting

Montreal, Quebec, Canada, H1T1C8

Principal Investigator: Jean-Claude Tardif, MD

Sub-Investigator: Philippe L L'Allier, MD

Sponsors and Collaborators

Montreal Heart Institute

Investigators

Principal Investigator: Jean-Claude Tardif, MD Montreal Heart Institute

Infarction will receive either colchicine (0.5 mg per day) or matching placebo (1:1 allocation ratio) for an estimated 2 years period or until the target of 301 primary endpoints has been reached.

Page 1 of 7

MURRAY & POOLE EXHIBIT 1006

EX2012, 14, 16

Cardiovascular Outcomes Trial
Reference: EudraCT no.: 2014-005172-28

MODEL AGREEMENT FOR NON-COMMERCIAL RESEARCH IN THE HEALTH SERVICE

This Agreement dated the date of last signature is between

Hampshire Hospitals NHS Foundation Trust, Aldermaston Road, Basingstoke, RG24 9NA,
(referred to as "the NHS Organisation")

AND

GREATER GLASGOW HEALTH BOARD constituted in terms of the National Health Service (Scotland) Act 1978 (as amended) and having its principal office at JB Russell House, Gartnavel Royal Hospital, 1055 Great Western Road, Glasgow G12 0XH (the "Health Board")

Montreal Heart Institute – 5000 Belanger east, Montreal, Quebec, H1T1C8

(referred to as "the Sponsor")

Which are collectively referred to as the "Parties" or individually referred to as a "Party"

The above Parties agree to the following obligations, terms and conditions when carrying out the clinical research study entitled Colchicine Cardiovascular Outcomes Trial (COLCOT) sponsored by the Montreal Heart Institute

CAN_DMS: 15132154217

Page 1 of 27

MHI EXHIBIT 2012

Page 1 of 28

Dr. Bouabdallaoui Disavows Inventorship

Q Are you the inventor or coinventor on any patent?

THE WITNESS: No, I'm not.

3. I did not develop the COLCOT study hypothesis and was not involved in conducting the main study. Along with the other listed co-authors, I worked on a secondary analysis of the study's results and participated in the writing of the article by Bouabdallaoui et al.

4. I do not consider myself an inventor of U.S. Patent No. 11,400,063 ("the '063 patent") (EX1001).

Applicable Law: Inventive Contributions



“Conception exists when a definite and permanent idea of an operative invention, including every feature of the subject matter sought to be patented, is known.”

Sewall v. Walters, 21 F.3d 411, 415 (Fed. Cir. 1994) (citations omitted).



“One does not qualify as a joint inventor by merely assisting the actual inventor after conception of the claimed inventions.”

Ethicon, Inc. v. United States Surgical Corp., 135 F.3d 1456, 1460 (Fed. Cir. 1998)
(citing *Sewall*, 21 F.3d at 416-17).

Inventive Contributions Only Came from Dr. Tardif

Q So whose idea was it to do the TTI post hoc analysis that is reported in this paper that is Exhibit 1005?

THE WITNESS: So, as mentioned previously, when the COLCOT study was published, we -- Dr. Tardif suggested to a number of the members of his team to discuss any ideas that can be -- that can come up from the -- from the database. So there were brainstormings, discussions within the team. These discussions were led by Dr. Tardif, and the -- the team was -- I was part of the team. I was working with him at that time.

Ground 4: Challenged Claims Are Not Obvious Over EX1005 and COLCRY5 (EX1016)

Challenged claims for Ground 4: 1-26, 28, and 40-50

Petitioner Has Not Carried Its Burden

- EX1005 is NOT prior art – cannot form basis for an obviousness challenge.
- COLCRYS (EX1016): discloses colchicine tablets indicated for treatment of diseases irrelevant to treating MI or reducing risk of stroke, and the methods claimed in the '063 patent.
 - No disclosure of early intervention after MI, without a pre-loading dose, patients with PCI, etc.
 - Cumulative of other prior art references disclosing colchicine tablets indicated for FMF (EX1002 at 317; EX1028 at 2).

Ground 2: COLCOT (EX1006) Does Not Anticipate The Identified Claims

Challenged claims for Ground 2: 27, 29-36, and 39

Petitioner Has Not Carried Its Burden to Show EX1006 Anticipates

- EX1006 was before the Examiner, or at very least “substantially the same reference.”
- EX1006 is not reliable:
 - Internal dating in the document is 18 months after Petitioner’s version.
 - EX2069 lists publicly available version as July 16, 2020.
- Petitioner’s expert, Dr. Ridker, admitted he never saw EX1006, would not rely on EX1006, and instead would rely on publicly available version.

Applicable Law: References Before Examiner



“Petitioner advances ground of unpatentability that are structured substantially identically to those previously considered by the Office, and relies on prior art that is similar to the art that the Office has considered on multiple prior occasions. We, therefore, conclude that the are and arguments presented in the Petition are substantially the same as those previously presented to the Office.”

Dropworks, Inc. v. The University of Chicago,
IPR2021-00100, Paper 9 at 13-14 (PTAB May 14, 2021).

Same Arguments from EX1006 Already Considered by Office

EX1006

https://web.archive.org/web/2017102004013/https://clinicaltrials.gov/ct2/show/NCT02551094 April 11, 2023 at 10:26 AM EDT CT02551094

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Colchicine Cardiovascular Outcomes Trial (COLCOT) (COLCOT)

This study is currently recruiting participants.

See [▶ Contacts and Locations](#)

Verified March 2017 by Montreal Heart Institute

Sponsor:
Montreal Heart Institute

ClinicalTrials.gov Identifier:
NCT02551094

First Posted: September 16, 2015
Last Update Posted: March 8, 2017

Information provided by (Responsible Party):
Montreal Heart Institute

▶ **Purpose**

The study evaluates whether long-term treatment with colchicine reduces rates of cardiovascular events in patients after myocardial infarction. Patients who have suffered a documented acute myocardial infarction within the last 30 days, are treated according to the national guidelines and after having completed any planned percutaneous revascularization procedures associated with their initial infarction will receive either colchicine (0.5 mg per day) or matching placebo (1:1 allocation ratio) for an estimated 2 years period or until the target of 301 primary endpoints has been reached.

Page 1 of 7

MURRAY & POOLE EXHIBIT 1006

EX1002

ClinicalTrials.gov Identifier: NCT02551094

Recruitment Status : Completed
First Posted : September 16, 2015
Results First Posted : October 19, 2020
Last Update Posted : October 19, 2020

Sponsor:
Montreal Heart Institute

Information provided by (Responsible Party):
Montreal Heart Institute

Certified by
Kathi
Performing the Functions and Duties of the
Under Secretary of Commerce
for Intellectual Property
and Director of the United States
Patent and Trademark Office

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MURRAY & POOLE EXHIBIT 1002

Dr. Ridker Did not Rely on EX1006

EX2071



Transcript of Paul Ridker, M.D.

Date: March 29, 2024

Case: Murray & Poole Enterprises, Ltd. -v- Institut de Cardiologie de Montreal

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Q Is there any reason that you believe that this is not the reflection of what would have been the updated version as of March 2017 when this is coming from October 20th of 2017?

A Oh, absolutely. Clintrials.gov is -- these -- these are brief summaries. We don't -- these are not the full, detailed -- I mean, I -- I don't have it here. May- -- maybe it's in one of these things here. Maybe not. I don't know.

But I mean, the full protocol is usually -- I mean, sometimes they go on to 150, 200, 300, you know, pages. This is -- this is -- this is, by definition, meant to be a website that people go to to, you know, do a quick search, what are -- what are people studying out there? And it's a website -- it's a very important website so that, you know, pharmaceutical companies can't hide what they're doing. So it's -- it's a public disclosure website, right? That's what its purpose is. But it's not meant to be definitive protocol.

The protocol is the other document, and it's -- and, again, you know, we say there it's -- that my opinion's based on an updated version, which is to me the -- again, if you want pull the updated version, we can go through that. That'd be fine.

EX1006 Does Not Anticipate Claim 27

EX1006

https://web.archive.org/web/20171020004013/https://clinicaltrials.gov/ct2/show/NCT02551094 April 11, 2023 at 10:26 AM EDT CT02551094

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The safety and scientific validity of this study is the responsibility of the study sponsor and investigators. Listing

Information provided by (Responsible Party):
Montreal Heart Institute

Full Text View Tabular View **No Study Results Posted**

national guidelines and after having completed any planned percutaneous revascularization procedures associated with their initial infarction will receive either colchicine (0.5 mg per day) or matching placebo (1:1 allocation ratio) for an estimated 2 years period or until the target of 301 primary endpoints has been reached.

Page 1 of 7 MURRAY & POOLE EXHIBIT 1006

Applicable Law: Inherency



“The mere fact that a certain thing may result from a given set of circumstances is not sufficient.”

PAR Pharm., Inc. v. TWI Pharm., Inc., 773 F.3d 1186, 1195 (Fed. Cir. 2014).



“An invitation to investigate is not an inherent disclosure.”

Metabolite Labs., Inc. v. Laboratory Corp. of Am. Holdings,
370 F.3d 1354, 1367 (Fed. Cir. 2004).

EX1006 Does Not Anticipate Claim 27 – No Inherency

EX1006

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This study is currently recruiting participants. ClinicalTrials.gov Identifier: NCT02551094
See [▶ Contacts and Locations](#) First Posted: September 16, 2015
Verified March 2017 by Montreal Heart Institute Last Update Posted: March 8, 2017
Sponsor:

Information provided by (Responsible Party):

Montreal Heart Institute

Full Text View

Tabular View

No Study Results Posted

▶ Purpose

The study evaluates whether long-term treatment with colchicine reduces rates of cardiovascular events in patients after myocardial infarction. Patients who have suffered a documented acute myocardial infarction within the last 30 days, are treated according to the national guidelines and after having completed any planned percutaneous revascularization procedures associated with their initial infarction will receive either colchicine (0.5 mg per day) or matching placebo (1:1 allocation ratio) for an estimated 2 years period or until the target of 301 primary endpoints has been reached.

Page 1 of 7

MURRAY & POOLE EXHIBIT 1006

EX2056

Circulation

ORIGINAL RESEARCH ARTICLE

Colchicine in Patients With Acute Coronary Syndrome The Australian COPS Randomized Clinical Trial

Editorial, see p 1901

David C. Tong, PhD
Jamie Layland, PhD

BACKGROUND: Inflammation plays a crucial role in clinical manifestations and complications of acute coronary syndromes (ACS). Colchicine, a commonly used treatment for gout, has recently emerged as a novel therapeutic option in cardiovascular medicine owing to its anti-inflammatory properties. We sought to determine the potential usefulness

In patients presenting with ACS, addition of colchicine to standard medical therapy did not significantly affect cardiovascular outcomes at 12 months and was associated with a higher rate of mortality.

396 assigned to the colchicine group and 399 to the placebo group. Over the 12-month follow-up, there were 24 events in the colchicine group compared with 38 events in the placebo group ($P=0.09$, log-rank). There was a higher rate of total death (8 versus 1; $P=0.017$, log-rank) and, in particular, noncardiovascular death in the colchicine group (5 versus 0; $P=0.024$, log-rank). The rates of reported adverse effects were not different (colchicine 23.0% versus placebo 24.3%), and they were predominantly gastrointestinal symptoms (colchicine, 23.0% versus placebo, 20.8%).

CONCLUSIONS: The addition of colchicine to standard medical therapy did not significantly affect cardiovascular outcomes at 12 months in patients with ACS and was associated with a higher rate of mortality.

REGISTRATION: URL: <https://www.anzctr.org.au>; Unique identifier: ACTRN12615000861550.

The full author list is available on page 1899.

Key Words: acute coronary syndrome
colchicine coronary artery disease
inflammation

Sources of Funding, see page 1899
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<https://www.ahajournals.org/journal/circ>

1890 November 17, 2020

Circulation. 2020;142:1890–1900. DOI: 10.1161/CIRCULATIONAHA.120.050771

Page 1 of 11

MHI EXHIBIT 2056

Study Protocols Should Not Be Anticipatory References

- Holding that study protocol—published months or even years before known results—anticipate a patent relating to study results would chill research and discovery.
- Regimen would create impossible framework of patenting what is unknowable based upon hypotheses; potentially eliminate method of treatment patents.



“An unbounded concept of inherency... threatens to stymie innovation by withdrawing from the realm of patentability that which has not before been known, used, or benefitted from.”

In re Montgomery, 677 F.3d 1375, 1383-84 (Fed. Cir. 2012).

Dependent Claims Are Not Anticipated by EX1006

- EX1006 does not disclose use of additional medications such as an antiplatelet agent, aspirin, or a statin as recited by claims 29-32.
- EX1006 does not disclose the patient has atherosclerotic coronary disease recited by claim 33.
- EX1006 does not disclose that the administration of colchicine is initiated upon assessment in (a) an ED, (b) the hospital, or (c) a medical office setting recited by claim 36.

Ground 3: Claims 1-50 Would Not Have Been Obvious

Asserted Prior Art Combination: Nidorf (EX1007); COLCOT (EX1006); ESC
Guidelines (EX1009); COLCRY5 (EX1016)

Cited References Are Same or Cumulative

- The same or substantially the same COLCOT protocol was before the Examiner (*compare* EX1006 with EX1002 at 315-23)
- EX1016 before the Examiner (EX1002 at 82, 126) and cumulative of other references (EX1002 at 317; EX1028 at 2)
- Related Nidorf patent (EX1018) with substantially the same disclosure was before the Examiner
- ESC Guidelines are general treatment references, and do not disclose use of colchicine.

Independent Claims 1 and 8 Would Not Have Been Obvious

- Petitioner's analysis relies on hindsight bias:
 - Plucking from Nidorf broad disclosures based on demonstrated results disclosed in '063 patent.
- Prior art as a whole fails to provide motivation/reasonable expectation of success for claims 1 and 8:
 - Claims 1 and 8: providing early intervention in treating MI patients who have had PCI.
- Field is highly unpredictable, not motivation to combine references:
 - Petitioner and its expert provide no argument showing motivation to combine references.
- Dependent claim limitations do not add obvious narrowing.

No Loading Dose Limitation

- No motivation or reasonable expectation for “no loading dose” limitation; prior art teaches away.
- Nidorf teaches “preferably” high loading dose of 1-2 mg on first day and 2-10 colchicine-free days after high loading dose before initiating low dose
- Loading dose was standard of care for colchicine administration at time of invention
- Prior art references do not mention omitting a loading dose.
- Efficacy and safety without loading dose was unknown.

EX1007 Motivated POSA to Use Loading Dose

EX1007

 US010206891B2	
(12) United States Patent Nidorf	(10) Patent No.: US 10,206,891 B2 (45) Date of Patent: *Feb. 19, 2019
(54) METHOD OF TREATING CARDIOVASCULAR EVENTS USING COLCHICINE CONCURRENTLY WITH AN ANTIPLATELET AGENT	2008/0039408 A1 2/2008 Freudenberg 2009/005158 A1 4/2009 Davis et al. 2009/0170952 A1 7/2009 Davis 2009/029915 A1 12/2009 Yang 2009/0312430 A1 12/2009 Sun et al. 2011/0046227 A1 2/2011 Davis 2011/0046228 A1 2/2011 Davis 2011/0190397 A1 8/2011 Davis 2013/0094322 A1 4/2013 Rafi 2013/0094323 A1 4/2013 Rafi
(71) Applicant: Murray and Poole Enterprises Limited, Gibraltar (GB)	
(72) Inventor: Mark Nidorf, Menora (AU)	
(73) Assignee: MURRAY AND POOLE ENTERPRISES LTD, Gibraltar (GB)	FOREIGN PATENT DOCUMENTS
(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(d) by 0 days. This patent is subject to a terminal dis- claimer.	CN 10393290 A 4/2007 CN 101485637 A 7/2009 CN 101485638 A 7/2009 CN 101560996 A 9/2009 CN 101732274 A 6/2010 JP 2009044224 A 2/2009 JP 2005153885 A 8/2005 JP 2011140498 A 7/2011 JP 2015197275 A 8/2012 JP 201226846 A 12/2012 JP 201510873 A 3/2013 WO 1993015282 A2 9/1993 WO 2003054329 A 7/2003 WO 2007040904 A2 4/2007 WO 2008131192 A2 10/2008 WO 2010046628 A1 4/2010 WO 2010103365 A 9/2010 WO 2011060256 A 5/2011 WO 2012100949 A1 8/2012 WO 2012100949 A 9/2012 WO 2013155478 A1 10/2013 WO 2016060944 A1 5/2014
(21) Appl. No.: 15/663,148	
(22) Filed: Jul. 28, 2017	
(65) Prior Publication Data US 2017/0326083 A1 Nov. 16, 2017	
Related U.S. Application Data	
(63) Continuation of application No. 14/603,049, filed on Jun. 22, 2015, now Pat. No. 9,744,144, which is a continuation-in-part of application No. PCT/AU2013/001261, filed on Nov. 1, 2013.	
(50) Foreign Application Priority Data	OTHER PUBLICATIONS
Nov. 2, 2012 (AU) 2012/904828	Adler et al., "Colchicine treatment for recurrent pericarditis: a decade of experience," <i>Circulation</i> , 97:2183-2185, 1998.
Nov. 5, 2012 (AU) 2012/904868	Antonopoulos et al., "Statins as Anti-inflammatory agents in Atherosclerosis: Molecular mechanisms and lessons from the recent clinical trials," <i>Curr. Pharma. Design</i> , 18:1519-1530, 2012.
(51) Int. Cl.	Crittenden, D. et al., "Colchicine Use Is Associated with decreased prevalence of Myocardial Infarction in Patients with Gout," <i>J. Rheumatol.</i> , 39:1458-1464, 2012.
A61K 31/165 (2006.01)	Finkelstein et al., "Colchicine for the prevention of Postpericardiotomy Syndrome," <i>Heart</i> , 270:751-754, 2002.
A61K 45/06 (2006.01)	Gabrielian, R.S., et al., "Comparative effects of losartan and losartan colchicines combination therapy in unstable angina patients with hyperuricemia," <i>Eur. J. Ischemic</i> , 7:583, 2006.
A61K 31/616 (2006.01)	(Continued)
A61K 31/37 (2006.01)	
A61K 31/4365 (2006.01)	
(52) U.S. Cl.	
CPC A61K 31/165 (2013.01); A61K 31/37 (2013.01); A61K 31/4365 (2013.01); A61K 31/616 (2013.01); A61K 45/06 (2013.01)	
(58) Field of Classification Search	Primary Examiner — Heidi Reese
None	(74) Attorney, Agent, or Firm — BioPharma Law Group, PLLC
See application file for complete search history.	
(56) References Cited	(57) ABSTRACT
U.S. PATENT DOCUMENTS	Methods of treating and/or preventing a cardiovascular event in a patient, the method comprising orally adminis- tering a colchicine to a patient who is receiving concurrent treatment with at least one antiplatelet agent, thereby treat- ing and/or preventing the cardiovascular event in the patient as provided.
3,173,876 A 3/1965 Zahrist 3,276,586 A 10/1966 Rosen 3,541,085 A 11/1970 Smithman et al. 3,541,086 A 11/1970 Bider et al. 3,546,142 A 12/1970 Michaels et al. 4,285,987 A 8/1981 Ayer et al. 8,415,395 B1 4/2013 Davis et al. 2002/0915735 A1 2/2002 Hedden 2006/0171046 A1 8/2006 Weinstein et al. 2006/0286108 A1 12/2006 Bell	

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31 Claims, No Drawings
MURRAY & POOLE EXHIBIT 1007

In a preferred embodiment, the amount/concentration of colchicine as used herein can be administered at the first day of administration in a higher dose (concentration/amount) compared to the administration of colchicine at the following day(s) of administration (maintenance administration/maintenance dose of administration). Alternatively such decreased dose (maintenance dose) can be started after 2, 3, 4, 5, 6, 7, 8, 9 or 10 days of initial administration of the higher dose. In case the course of treatment is any such as described above, the higher dose/amount/concentration of colchicine (e.g. at the first day of administration) can be any as described above, provided that the maintenance dose (the dose/amount/concentration of colchicine at the days following the higher dose/amount/concentration) is lower than the initial dose/amount/concentration of colchicine (e.g. at the first day of administration). Preferably, the composition of the invention is administered with a dose of colchicine of between about 1.0 mg to about 2.0 mg at the first day (preferably as a single dose) of administration and the maintenance dose of colchicine at the following day(s) of administration is between about 0.5 mg to about 1.0 mg.

Loading Dose Was Standard of Care in 2019

EX1040

Coronary Heart Disease

Anti-Inflammatory Treatment With Colchicine in Acute Myocardial Infarction A Pilot Study

Spyridon Deftereos, MD*; Georgios Giannopoulos, MD*; Christos Angelidis, MD*

After completion of the diagnostic coronary angiography, patients were randomly assigned (using a 1:1 allocation scheme based on a computer-generated randomization algorithm – an R language script was used for this purpose) to receive colchicine, starting with 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 (Figure 1). Patients with <60 kg body weight received 0.5 mg once daily. Monitoring of adverse events focused on gastrointestinal manifestations, hepatotoxicity, myelotoxicity, and myotoxicity. Operators and personnel involved in patient follow-up and management were blinded as to patient allocation (patient treatment was identified by a serial number; assignment records were kept in a digital file that was unlocked after conclusion of the last patient follow-up procedures and database locking).

Received May 20, 2015; accepted August 5, 2015.
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MURRAY & POOLE EXHIBIT 1040

EX2005

Patients were randomized to receive a conventional treatment with aspirin 800 mg orally every 6 or 8 hours for 7 to 10 days with gradual tapering over 3 to 4 weeks (group I) or a treatment with aspirin at the same dose combined with colchicine 1.0 to 2.0 mg for the first day and then a maintenance dose of 0.5 to 1.0 mg daily for 3 months (group II). The lower dose (initial dose 1.0 mg and maintenance dose 0.5 mg daily) was given to patients who weighed <70 kg or who were intolerant to the highest dose (initial dose 1.0 mg BID and maintenance dose of 0.5 mg BID). Randomization was based on permuted blocks, with a block size of 4.

then 0.5-1.0 mg/d for 6 months). When aspirin was contraindicated, prednisone (1.0-1.5 mg/kg daily) was given for 1 month and then was gradually tapered. The primary end point was the recurrence rate. Intention-to-treat analyses were performed by treatment group.

PERICARDITIS IS THE MOST troublesome complication of acute pericardial effusion, occurring in 17% to 58% of patients.¹ It is generally a self-limiting disease, but the optimal treatment for "proven" cases has not been established. The diagnosis is often difficult to make in the present setting (such as cardiac tamponade). The differential diagnosis includes malignancy; infectious etiologies are nonspecific; and include noninfectious, idiopathic, and autoimmune etiologies. Anticardiolipin inflammatory drugs, corticosteroids, and pericardectomy.²⁻⁵ Although most patients with pericarditis respond to nonsteroidal anti-inflammatory drugs, others are prolonged course and respond only to corticosteroids. The purpose of this review is to compare the efficacy of frequent administration of corticosteroids with the use of nonsteroidal anti-inflammatory drugs, and to review evidence for corticosteroid dependence and

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To our knowledge, no clinical trial has tested the effects of colchicine as the first-choice drug for the treatment of the first recurrence of pericarditis. The aims of this work are to verify the safety and efficacy of colchicine therapy as an adjunct to conventional therapy for the first episode of recurrence and to verify whether the natural history of the disease may change because of the early use of colchicine. No characteristics of the first episode have been reported to predict the likelihood of recurrences.^{2,28,29}

Several small studies^{4,9-21} have successfully used colchicine to prevent acute pericarditis recurrences after failure of conventional therapy. The efficacy of colchicine in the prevention of pericarditis recurrences may change because of the early use of colchicine. No characteristics of the first episode have been reported to predict the likelihood of recurrence.^{2,4,6,9,22}

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EX2007

Annals of Internal Medicine

ORIGINAL RESEARCH

Colchicine for Recurrent Pericarditis (CORP)

A Randomized Trial

Massimo Iezzoni, MD; Antonio Bruscia, MD; Roberto Cemin, MD; Stefania Ferras, MD; Riccardo Belli, MD; Silvia Maestroni, MD; Rita Trinchero, MD; David H. Spodick, MD; and Yehuda Adler, MD, on behalf of the CORP (Colchicine for Recurrent Pericarditis) Research Group

Objective: To evaluate the efficacy and safety of colchicine for the secondary prevention of recurrent pericarditis.

Design: Prospective, randomized, double-blind, placebo-controlled multicenter trial. (ClinicalTrials.gov registration number: NCT00128414)

Setting: 4 general hospitals in urban areas of Italy

Intervention: In addition to conventional treatment, patients were randomly assigned to receive either placebo or colchicine, 1.0 to 2.0 mg on the first day followed by a maintenance dose of 0.5 to 1.0 mg/d, for 6 months.

Measurements: The primary study end point was the recurrence rate at 18 months. Secondary end points were symptom persistence at 72 hours, remission rate at 1 week, number of recurrences, time to first recurrence, disease-related hospitalization, cardiac tamponade, and rate of constrictive pericarditis.

Results: At 18 months, the recurrence rate was 24% in the colchicine group and 55% in the placebo group (absolute risk reduction, 0.31 [95% CI, 0.13 to 0.46]; relative risk reduction, 0.56 [95% CI, 0.27 to 0.73]; number needed to treat, 3 [95% CI, 2 to 7]). Colchicine reduced the persistence of symptoms at 72 hours (absolute risk reduction, 0.30 [95% CI, 0.13 to 0.45]; relative risk reduction, 0.56 [95% CI, 0.27 to 0.74]) and mean number of recurrences, increased the remission rate at 1 week, and prolonged the time to subsequent recurrence. The study groups had similar rates of side effects and drug withdrawal.

Limitation: Multiple recurrences and neoplastic or bacterial cause were excluded.

Conclusion: Colchicine is safe and effective for secondary prevention

tion of recurrent pericarditis.

Ann Intern Med. 2011;155:409-414. www.annals.org

This article was published at www.annals.org on 28 August 2011.

Recurrent pericarditis is probably the most common antithrombotic complication of acute pericarditis, occurring in 10% to 30% of patients with a first episode of acute pericarditis (1–3). The recurrence rate increases up to 50% after a first recurrence (4). Colchicine has shown promise for the secondary prevention of recurrent pericarditis in observational studies (5–7) and in the CORE (Colchicine for REcurrent pericarditis) trial (4), an open-label, single-center, randomized trial in which the drug halved the recurrence rate. Low dosages of colchicine (0.5 to 1.0 mg/d) seem to be safe and effective for treating pericarditis (1,4,8). However, no multicenter, double-blind, randomized trial has confirmed these favorable preliminary findings. This new effort, the CORE-2 study, is promising. But the

Setting and Participants

We enrolled 120 patients with a first recurrence of pericarditis from 4 general hospitals in Italy (Maria Vittoria Hospital, Torino; Ospedali Riuniti, Bergamo; San Maurizio Regional Hospital, Bolzano; and Ospedale San Annunziata, Savigliano). All consecutive patients with a first recurrence of pericarditis were assessed for potential enrollment. Pericarditis was diagnosed by using available published criteria (1, 4, 10, 11), which include typical pericardial chest pain, pericardial friction rubs, widespread ST-segment elevation or PR-segment depression that was not previously reported, and new or worsening pericardial effusion on echocardiography. A clinical diagnosis of acute pericarditis was made when at least 2 of these criteria were

Intervention: In addition to conventional treatment, patients were randomly assigned to receive either placebo or colchicine, 1.0 to 2.0 mg on the first day followed by a maintenance dose of 0.5 to 1.0 mg/d, for 6 months.

MHI EXHIBIT 2007

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Dr. Ardehali Confirmed Standard of Care of Colchicine

Q. And what is a safe amount of colchicine to be taken on a daily basis?

A. -- the dosage we have available in this country is .6 milligrams. So in Europe, it's .5 milligrams. In our patients with pericarditis, we usually give them a loading dose, so it's usually 1.2 milligram loading dose, sometimes even higher. And depending on how they tolerate, we maintain them on .6 milligrams after the loading dose.

Q. Why do you give a loading dose with pericarditis?

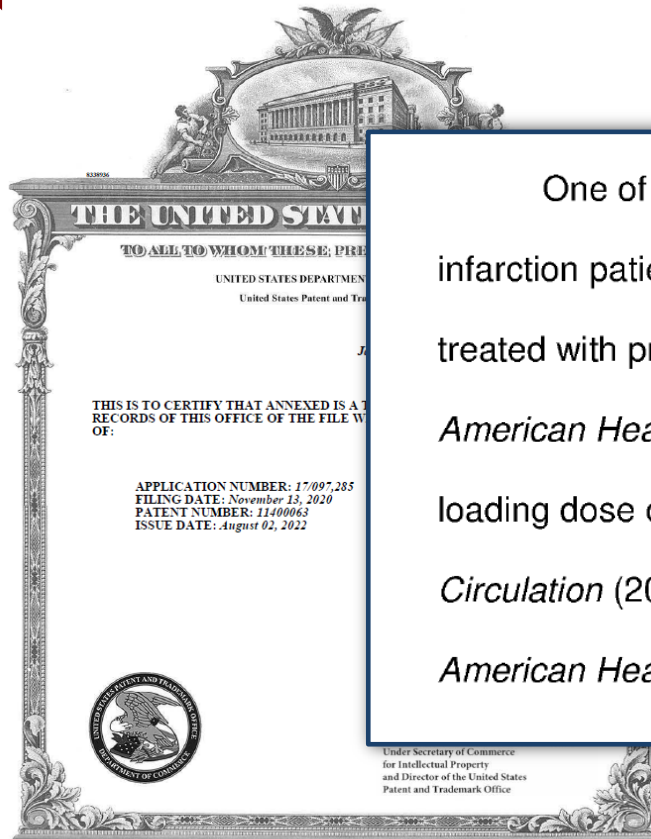
A. When?

Q. Why?

A. So the idea here is to attack inflammation as effectively as possible. So the idea is to give a loading dose to make sure that the inflammation is under control and then maintain it with a maintenance dose.

Examiner Found No Motivation to Remove Loading Dose

EX1007



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MURRAY & POOLE EXHIBIT 1002

One of ordinary skill would not have found it obvious to treat the myocardial infarction patients of *Circulation* (2015), 132(15), pp. 1395-1403, who have also been treated with primary percutaneous coronary intervention, following the method of *American Heart Journal* (September 2019), Vol. 215, pp. 62-69 – that is, without a loading dose of colchicine. There is no motivation to delete the loading dose of *Circulation* (2015), 132(15), pp. 1395-1403 and treat these patients by the method of *American Heart Journal* (September 2019), Vol. 215, pp. 62-69.

3-5 Day Administration

- No motivation/reasonable expectation of success regarding administration within 3-5 days after MI.
 - Nidorf teaches initiating colchicine to patients that were stable for six months after an MI.
 - No expectation from results administering 30 or 60 days after MI.
 - ESC Guidelines relate to administration of other drugs.
- Other studies showed no benefit in MI treatment over placebo.
- Examiner found no motivation to treat patients who have already received PCI without loading dose.

EX1007 Did NOT Motivate Early Administration

EX1007

 US010206891B2	
(12) United States Patent Nidorf	(10) Patent No.: US 10,206,891 B2 (45) Date of Patent: *Feb. 19, 2019
(54) METHOD OF TREATING CARDIOVASCULAR EVENTS USING COLCHICINE CONCURRENTLY WITH AN ANTIPLATELET AGENT	2008/0039408 A1 2/2008 Freudenberg 2009/0051548 A1 4/2009 Davis et al. 2009/0170952 A1 7/2009 Davis 2009/0209155 A1 12/2009 Yang 2009/0312430 A1 12/2009 Sun et al. 2011/0046227 A1 2/2011 Davis 2011/0046228 A1 2/2011 Davis 2011/0190397 A1 8/2011 Davis 2013/0094322 A1 4/2015 Rafi 2013/0094323 A1 4/2015 Rafi
(71) Applicant: Murray and Poole Enterprises Limited, Gibraltar (GB)	
(72) Inventor: Mark Nidorf, Menora (AU)	
(73) Assignee: MURRAY AND POOLE ENTERPRISES LTD, Gibraltar (GB)	FOREIGN PATENT DOCUMENTS
(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(d) by 0 days. This patent is subject to a terminal disclaimer.	CN 1939290 A 4/2007 CN 101485637 A 7/2009 CN 101485638 A 7/2009 CN 101506996 A 9/2009 CN 101732274 A 6/2010 JP 200904224 A 2/2009 JP 200515385 A 8/2005 JP 2011140498 A 7/2011 JP 2015197725 A 8/2012 JP 201226846 A 12/2012 JP 201510873 A 3/2013 WO 1993015282 A2 8/1993 WO 2003054329 A 7/2003 WO 2007040904 A2 4/2007 WO 2008131192 A2 10/2008 WO 2010046628 A1 4/2010 WO 2010103365 A 9/2010 WO 2011060256 A 5/2011 WO 2012100949 A1 8/2012 WO 2012100949 A 9/2012 WO 2013155478 A1 10/2013 WO 2016060944 A1 5/2014
(21) Appl. No.: 15/663,148	
(22) Filed: Jul. 28, 2017	
(65) Prior Publication Data US 2017/0326083 A1 Nov. 16, 2017	OTHER PUBLICATIONS
Related U.S. Application Data (63) Continuation of application No. 14/603,049, filed on Jun. 22, 2015, now Pat. No. 9,744,144, which is a continuation-in-part of application No. PCT/AU2013/001261, filed on Nov. 1, 2013.	Adler et al., "Colchicine treatment for recurrent pericarditis: a decade of experience," <i>Circulation</i> , 97:2183-2185, 1998. Antonopoulos et al., "Statins as Anti-inflammatory agents in Atherogenesis: Molecular mechanisms and lessons from the recent clinical trials," <i>Curr. Pharma. Design</i> , 18:1519-1530, 2012. Critchenden, D. et al., "Colchicine Use Is Associated with decreased prevalence of Myocardial Infarction in Patients with Gout," <i>J. Rheumatol.</i> , 39:1458-1464, 2012. Finkelstein et al., "Colchicine for the prevention of Postpericardiotomy Syndrome," <i>Heart</i> , 270:751-754, 2002. Gabrielian, R.S., et al., "Comparative effects of losartan and losartan colchicine combination therapy in unstable angina patients with hyperuricemia," <i>Eur. J. Ischemic</i> , 7:583, 2006. (Continued)
(50) Foreign Application Priority Data Nov. 2, 2012 (AU) 2012/904828 Nov. 5, 2012 (AU) 2012/904808	
(51) Int. Cl. A61K 31/165 (2006.01) A61K 45/06 (2006.01) A61K 31/616 (2006.01) A61K 31/37 (2006.01) A61K 31/4365 (2006.01) (52) U.S. Cl. CPC A61K 31/165 (2013.01); A61K 31/37 (2013.01); A61K 31/4365 (2013.01); A61K 31/616 (2013.01); A61K 45/06 (2013.01)	
(58) Field of Classification Search None See application file for complete search history.	<i>Primary Examiner</i> — Heidi Reese (74) <i>Attorney, Agent, or Firm</i> — BioPharma Law Group, PLLC
(56) References Cited U.S. PATENT DOCUMENTS 3,173,876 A 3/1965 Zahrist 3,276,586 A 10/1966 Rosen 3,541,005 A 11/1970 Simhauman et al. 3,541,006 A 11/1970 Bider et al. 3,546,142 A 12/1970 Michaels et al. 4,285,987 A 8/1981 Ayer et al. 8,415,395 B1 4/2013 Davis et al. 2002/0015735 A1 2/2002 Hedden 2006/0171948 A1 8/2006 Weinstein et al. 2006/0286108 A1 12/2006 Bell	(57) ABSTRACT Methods of treating and/or preventing a cardiovascular event in a patient, the method comprising orally administering a colchicine to a patient who is receiving concurrent treatment with at least one antiplatelet agent, thereby treating and/or preventing the cardiovascular event in the patient are provided.

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31 Claims, No Drawings
MURRAY & POOLE EXHIBIT 1007

It was planned to recruit a study population that would include 500 patients planned (532 patients randomized as 32 dropped out early), 250 randomized to the control group and 250 patients randomized to treatment who were tolerant of colchicine for at least 4 weeks after the date of their randomization. Patients were eligible for inclusion if they met each of the following criteria: 1) angiographically proven coronary disease; 2) aged 35 to 85 years; 3) clinically stable for at least 6 months, 4) no major competing comorbidities or contra-indication to colchicine therapy, 5) considered to be compliant with therapy and attending routine cardiology follow up appointments, and 6) willing to be consented and randomized into the study. Patients with a history of bypass surgery were only eligible if they had undergone bypass surgery more than 10 years before, or had angiographic evidence of graft failure or had undergone stenting since their bypass surgery. All patients signed informed consent before randomization.

Claims 27-39 Would NOT Have Been Obvious

- No motivation to combine references or reasonable expectation of success from prior art that administration of colchicine would reduce risk of stroke.
- COLCRYST, COLCOT, Nidorf, and ESC Guidelines do not mention reduction in risk of stroke – different indications/drugs.
 - Nidorf's administration only to stable patients does not provide motivation.
 - Claim as a whole not disclosed by COLCOT.

Applicable Law: Objective Evidence



“The objective indicia of non-obviousness play an important role as a guard against the statutorily proscribed hindsight reasoning in the obviousness analysis.”

WBIP, LLC v. Kohler Co., 829 F.3d 1317, 1328 (Fed. Cir. 2016).

Objective Evidence Supports Nonobviousness

- Unexpected benefit to administer colchicine within 3 days or within 5 days after MI = 25% reduction in risk of future CV event; 75% reduction in risk of stroke.
- POSA would have been skeptical that initiating low-dose colchicine without a pre-loading dose to patients within 3 days after an MI would reduce risk of any CV events, including stroke.
- EX1005 is not prior art; references before patent office.

Loading Dose Was Standard of Care in 2019

EX2055



CLINICAL RESEARCH

COLIN trial: Value of colchicine in the treatment of patients with acute myocardial infarction and inflammatory response



The lack of effect of colchicine in our study could be explained by late administration in the intensive care unit after the reperfusion and without a loading dose.

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Received 10 April 2016; received in revised form 13 October 2016; accepted 17 October 2016
Available online 3 January 2017

KEYWORDS
Colchicine;
Cardiovascular
disease;

Summary
Background. – Inflammation is involved during acute myocardial infarction, and could be an interesting target to prevent ischaemia-reperfusion injuries. Colchicine, known for its pleiotropic anti-inflammatory effects, could decrease systemic inflammation in this context.

Abbreviations: AMI, Acute myocardial infarction; CRP, C-reactive protein; hs-cTnT, High-sensitivity cardiac troponin T; LAD, Left anterior descending; MRI, Magnetic resonance imaging; PCI, Percutaneous coronary intervention; STEMI, ST-segment elevation myocardial infarction; TMI, Thrombolysis in myocardial infarction.

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<http://dx.doi.org/10.1016/j.acvd.2016.10.004>
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MHI EXHIBIT 2055

EX1040



European Heart Journal (2020) 41, 4092–4099
doi:10.1093/eurheartj/ehaa659

FAST TRACK CONGRESS
Intensive cardiac care and acute coronary syndromes

Time-to-treatment initiation of colchicine and cardiovascular outcomes after myocardial

Colchicine at the low dose of 0.5 mg daily was shown to significantly reduce the risk of ischaemic CV events by 23% compared with placebo when initiated within the first 30 days after MI in the COLchicine Cardiovascular Outcomes Trial (COLCOT).⁹

Keywords: colchicine, myocardial infarction, time-to-treatment initiation, cardiovascular outcomes, COLCOT.
See page 4100 for the editorial comment on this article (doi:10.1093/eurheartj/ehaa752)

Aims

The COLchicine Cardiovascular Outcomes Trial (COLCOT) demonstrated the benefits of targeting inflammation after myocardial infarction (MI). We aimed to determine whether time-to-treatment initiation (TTI) influences the beneficial impact of colchicine.

Methods and results

In COLCOT, patients were randomly assigned to receive colchicine or placebo within 30 days post-MI. Time-to-treatment initiation was defined as the length of time between the index MI and the initiation of study medication. The primary efficacy endpoint was a composite of cardiovascular death, revascularized cardiac arrest, MI, stroke, or urgent hospitalization for angina requiring coronary revascularization. The relationship between endpoints and various TTI (<3, 4–7 and >8 days) was examined using multivariable Cox regression models. Amongst the 4661 patients included in this analysis, there were 1193, 720, and 2748 patients, respectively, in the three TTI strata. After a median follow-up of 22.7 months, there was a significant reduction in the incidence of the primary endpoint for patients in whom colchicine was initiated < Day 3 compared with placebo [hazard ratios (HR) = 0.52, 95% confidence intervals (CI) 0.32–0.84]. In contrast to patients in whom colchicine was initiated between Days 4 and 7 (HR = 0.96, 95% CI 0.53–1.75) or > Day 8 (HR = 0.82, 95% CI 0.61–1.11). The beneficial effects of early initiation of colchicine were also demonstrated for urgent hospitalization for angina requiring revascularization (HR = 0.35).

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MURRAY & POOLE EXHIBIT 1005