

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

MURRAY & POOLE ENTERPRISES LTD.,
Petitioner,

v.

INSTITUT DE CARDIOLOGIE DE MONTREAL,
Patent Owner.

Case IPR2023-01064
Patent No. 11,400,063

PETITION FOR *INTER PARTES* REVIEW

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CLAIM LISTING

Claim limitations
1[a]. A method of treating a patient after having a myocardial infarction (MI),
1[b]. the method comprising initiating the administration of colchicine at a daily low dose to the patient...,
1[c] wherein the colchicine is administered without pre-loading the patient with a higher dose of colchicine before the administration at the daily low dose,
1[d] within about 3 days of the MI
1[e] wherein percutaneous coronary intervention was performed for treating the patient's MI.
2. The method according to claim 1, wherein the patient was prescribed a medication.
3. The method according to claim 2, wherein the medication is an antiplatelet agent.
4. The method according to claim 2, wherein the medication is aspirin.
5. The method according to claim 2, wherein the medication is a statin.
6. The method according to claim 1, wherein the patient is at a lower risk of a cardiovascular event, relative to a patient not being administered colchicine.

7. The method according to claim 6, wherein the cardiovascular event is an ischemic cardiovascular event.

8[a]. A method of treating a patient alter having a myocardial infarction (MI),

8[b] the method comprising initiating the administration of colchicine at a daily low dose to the patient...,

8[c] wherein the colchicine is administered without pre-loading the patient with a higher dose of colchicine before the administration at the daily low dose,

8[d] within about 3 days of the MI

8[e] 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.

9. The method according to claim 6, wherein the cardiovascular event is myocardial infarction.

10. The method according to claim 8, wherein the cardiovascular event is stroke.

11. The method according to claim 8, wherein the cardiovascular event is urgent hospitalization for angina requiring coronary revascularization.

12. The method according to claim 1, wherein the patient has atherosclerotic coronary artery disease.

13. The method according to claim 1, wherein the administration of colchicine is initiated upon assessment in (a) an emergency department (ED), (b) the hospital, or (c) a medical office setting.
14. The method according to claim 1, wherein the colchicine is in the form of a tablet.
15. The method of claim 14, wherein the tablet is coated.
16. The method of claim 15, wherein the tablet is film-coated.
17. The method according to claim 1, wherein the colchicine is administered at 0.3 to 0.7 mg.
18. The method according to claim 17, wherein the colchicine is administered at 0.4 to 0.6 mg.
19. The method according to claim 18, wherein the colchicine is administered at 0.5 mg.
20. The method according to claim 8, wherein the colchicine is administered at 0.5 mg.
21. The method according to claim 9, wherein the colchicine is administered at 0.5 mg.
22. The method according to claim 10, wherein the colchicine is administered at 0.5 mg.

23. The method according to claim 11, wherein the colchicine is administered at 0.5 mg.
24. The method according to claim 1, wherein the colchicine is administered once, twice or three times a day.
25. The method according to claim 24, wherein the colchicine is administered once per day.
26. The method according to claim 1, wherein the patient is an adult human.
27 [a] A method of reducing the risk of a stroke in a patient after having an MI, 27 [b] the method comprising initiating the administration of colchicine at a daily low dose to the patient 27[c] within about 30 days of an MI.
28. The method according to claim 27, wherein the method comprises administering colchicine within 4 to 7 days of the MI.
29. The method according to claim 27, wherein the patient was prescribed a medication.
30. The method according to claim 29, wherein the medication is an antiplatelet agent.
31. The method according to claim 29, wherein the medication is aspirin.
32. The method according to claim 29, wherein the medication is a statin.

33. The method according to claim 27, wherein the patient has atherosclerotic coronary artery disease.
34. The method according to claim 27, wherein the colchicine is administered at 0.5 mg.
35. The method according to claim 27, wherein the colchicine is administered once per day.
36. The method according to claim 27, wherein the administration of colchicine is initiated upon assessment in (a) an emergency department (ED), (b) the hospital, or (c) a medical office setting.
37. The method according to claim 27, wherein the colchicine is in the form of a coated tablet.
38. The method of claim 37, wherein the tablet is film-coated.
39. The method of claim 27, wherein the patient is an adult human.
40. The method according to claim 8, wherein the patient was prescribed a medication.
41. The method according to claim 40, wherein the medication is an antiplatelet agent.
42. The method according to claim 40, wherein the medication is aspirin.
43. The method according to claim 40, wherein the medication is a statin.

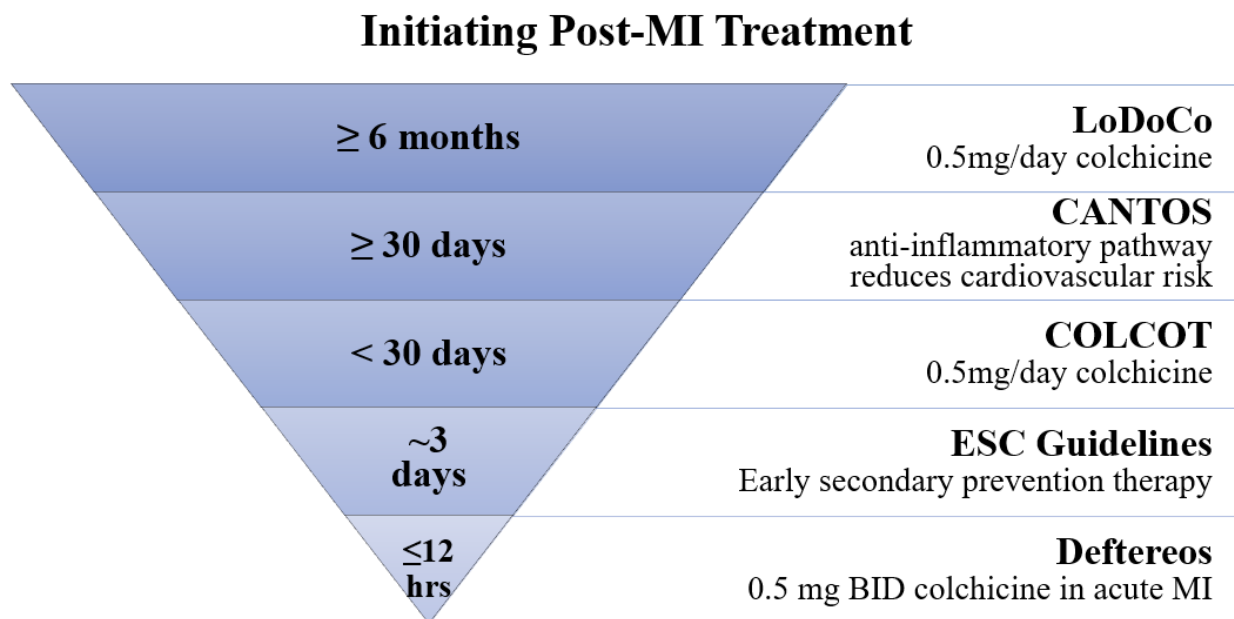
44. The method according to claim 8, wherein the patient has atherosclerotic coronary artery disease.
45. The method according to claim 8, wherein the colchicine is administered once per day.
46. The method according to claim 8, wherein the administration of colchicine is initiated upon assessment in (a) an emergency department (ED), (b) the hospital, or (c) a medical office setting.
47. The method according to claim 8, wherein the colchicine is in the form of a coated tablet.
48. The method of claim 47, wherein the tablet is film-coated.
49. The method of claim 8, wherein the patient is an adult human.
50. The method of claim 8, wherein the cardiovascular event is resuscitated cardiac arrest.

I. INTRODUCTION

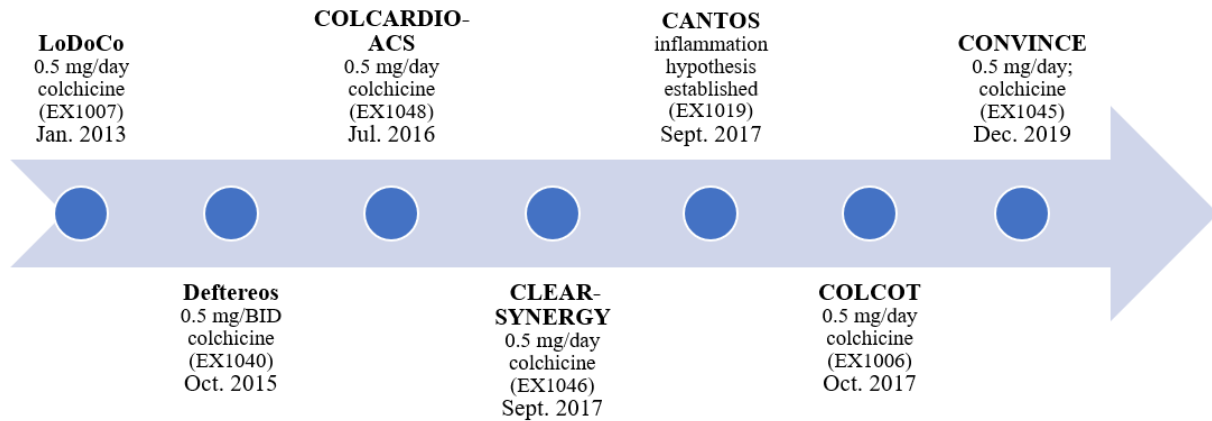
U.S. Patent 11,400,063 (“the ’063 patent”), “Early Administration of Low-Dose Colchicine After Myocardial Infarction,” claims administering daily low doses of colchicine, such as 0.5 mg/day, to patients within 30 days following a myocardial infarction (“MI”) based on the “COLCOT” study. It also claims initiating colchicine administration “within about 3 days” or “within 4 to 7 days” of an MI based on a COLCOT *post hoc* analysis added in its November 13, 2020, non-provisional application.

Colchicine is a centuries-old anti-inflammatory medication, FDA-approved in film-tablet form as COLCRYS™ (EX1016) for the treatment of gout and Familial Mediterranean fever (FMF). Long before the ’063 patent’s earliest possible priority date, the completed “LoDoCo” clinical trial (EX1007) had shown 0.5 mg/day colchicine to be effective in coronary artery disease patients, including those having suffered an MI, to reduce the risk of subsequent cardiovascular events such as stroke. Results from the “CANTOS” trial in MI-patients (EX1019) then validated the “anti-inflammatory hypothesis” of coronary artery disease, conclusively demonstrating that inhibiting certain inflammatory pathways (also inhibited by colchicine) reduced secondary cardiovascular events in MI patients. COLCOT Protocol (EX1006) specifically taught initiating colchicine treatment within 30 days of an MI, and ESC Guidelines (EX1009) recommended initiating secondary prevention therapy prior to

post-MI hospitalization discharge, from which initiating colchicine “within about 3 days” or “within 4 to 7 days” post-MI would have been obvious. Notably, Deftereos (EX1040) had already tested and shown initiating acute low-dose colchicine treatment within 12 hours post-MI to be safe. Taken together, these studies point directly towards the claimed treatment.



The movement towards early, low-dose colchicine treatment is further reflected in multiple other low dose colchicine clinical studies designed to reduce cardiovascular events in patients with recent acute MI or stroke, including CONVINCe (EX1045), CLEAR-SYNERGY (EX1046), and COLCARIO-ACS (EX1048).



All claims are anticipated and/or obvious by express disclosures of the identical colchicine treatment methods and/or the clinical practice and trend to early initiation of secondary preventive therapy of MI patients.

The *post hoc* COLCOT analysis, on which the claims reciting initiating treatment “within about 3 days” and “within 4 to 7 days” are based, was also previously published by nearly two dozen researchers in Bouabdallaoui (EX1005) and further presented publicly. Bouabdallaoui anticipates and/or in combination with COLCRYS renders obvious all these claims.

Institution is warranted in view of uncited and unaddressed new evidence and arguments, and numerous errors by the Examiner, including selecting the wrong closest prior art and allowing the '063 patent based on elements wrongly believed to be missing from the prior art. Evidencing the Examiner's errors, Patent Owner did not even contest after similar claims in its related EP application were found to lack novelty over prior art, including LoDoCo.

II. BACKGROUND AND ASSERTED PRIOR ART

A. Myocardial Infarction

Myocardial infarction (MI) was recognized as “the most severe manifestation of coronary artery disease,” and atherosclerosis was known to be its “most common cause.” EX1017, 1; EX1015, 1; EX1006, 4; EX1049, ¶23. Treatment begins with emergency/urgent management to restore blood flow, typically using percutaneous coronary intervention (PCI) within 0 to 12 hours, which does not, however, resolve the underlying chronic and progressive atherosclerotic coronary artery disease. EX1049, ¶24. EX1021, 4; EX1010, 1.

Because MI patients remained at very high risk for recurrent cardiovascular events despite PCI treatment, long-term secondary prevention therapy, such as statins, was common. EX1049, ¶¶25, 26; *see also* EX1017, 9; EX1007, 2:34-36; EX1009, 31. Secondary prevention treatments were initiated as soon as practical—typically by about 2 to 3-days post-MI, when the patients are stabilized and ready for hospitalization discharge. EX1049, ¶¶61-63; EX1014, 1; EX1011, 1; EX1009, 13, 24. It was understood that failure to initiate secondary preventatives prior to discharge was associated with “[l]ow treatment adherence” and “worse outcomes.” EX1009, 30; EX1049, ¶61.

B. Anti-inflammatory Agents Had Been Successfully Used to Reduce Risks of Cardiovascular Events as of 2019

Colchicine was a well-known anti-inflammatory medication used for the treatment of gouty arthritis, FMF, and Behcet's disease. EX1007, 1:26-28; EX1049, ¶27. By 2019, daily low doses had also been shown to provide successful secondary preventive therapy for coronary artery disease and were in widespread testing for atherosclerotic conditions generally. EX1049, ¶¶26-53.

1. LoDoCo Trial

The LoDoCo ("Low-Dose Colchicine") trial had evaluated using 0.5 mg/day colchicine to reduce cardiovascular event risks in patients with stable coronary artery disease, including patients who had suffered an MI at least 6 months previously. EX1020, 11, Table 1; EX1049, ¶27. Published in 2013, LoDoCo's results demonstrated "*significant reduction off the risk of a cardiovascular event, including ACS, out-of-hospital cardiac arrest, and noncardioembolic ischemic stroke,*" and provided the first clinical evidence of colchicine's efficacy in preventing cardiovascular events in patients with underlying coronary disease, including those who had MI.¹ EX1020, 13, 15; EX1022, 3 (citing EX1020) (named inventor Tardif of the '063 patent acknowledging LoDoCo's earlier treatment of patients with stable coronary disease); EX1049, ¶¶28-29.

¹ All ***bold italic*** emphasis is added.

Inspired by LoDoCo, the art recognized the “increasing evidence support[s] a potentially beneficial role for colchicine therapy in prevention of cardiovascular disease (CVD)” and that “colchicine may be an attractive option to serve this need [for new agents for secondary prevention post-ACS].” EX1029, 2, 8; EX1030, 11 (acknowledging “the apparently beneficial effects of colchicine for prevention of cardiovascular events” in view of LoDoCo data); EX1026, 4 (noting that LoDoCo “strongly suggest[ed] a marked benefit” of low-dose colchicine); EX1042, 9 (LoDoCo showed that “[c]olchicine significantly reduced the incidence of a combined adverse cardiovascular end point”); EX1043, 2; EX1026, 3 (concluding that LoDoCo demonstrated that “low-dose colchicine (0.5 mg/day) in patients on high-dose statins was well tolerated and was strongly suggestive of a marked benefit.”); EX1044, 3; EX1049, ¶29.

2. COLCOT Trial Design

COLCOT (“Colchicine Cardiovascular Outcomes Trial”) was similarly directed to long-term use of 0.5 mg/day colchicine to reduce the risk of cardiovascular events, such as stroke. EX1006, 1; EX1049, ¶30. COLCOT differed from LoDoCo in that: (1) it was limited to patients with recent MI after completion of any planned PCI, and (2) colchicine administration was initiated within 30 days of the MI rather than after at least 6 months. *Compare* EX1006, 1, 2, 5 with EX1020, 11, Table 1; EX1049, ¶¶31-33.

3. CANTOS

Confidence in treating coronary artery disease with colchicine was reinforced by Dr. Ridker's large-scale placebo-controlled CANTOS (Canakinumab Anti-Inflammatory Thrombosis Outcomes Study), proving in 2017 the so-called "inflammation hypothesis" of cardiovascular disease. EX1049, ¶34. As Dr. Ridker reported, targeting inflammatory pathways in patients with histories of MI at least 30 days before randomization significantly lowered the rate of recurrent cardiovascular events, including nonfatal myocardial infarction, nonfatal stroke, and cardiovascular death. EX1019, 2, 4, 6, 12; EX1049, ¶¶35-36.

CANTOS bolstered confidence in treating MI patients with other anti-inflammatory secondary prevention agents, such as colchicine, which impacts the same canonical NLRP3/interleukin-1 inflammatory pathways. EX1026, 4, Figure 1; EX1041, 1; EX1049, ¶36. This was reflected in the literature, which recognized that "[w]ith the publication of the CANTOS results, clinicians have *definitive evidence that directly targeting inflammation is beneficial for the secondary prevention of cardiovascular disease.*" E.g., EX1017, 5. For this reason, it was praised as "a giant leap for vascular biology," "a gigantic proof-of-concept trial," "a new calculus of inflammasome targeting for vascular protection," a study that "validates the inflammatory pathogenesis of atherosclerosis," and a trial that opens "a new chapter

in therapeutic targeting.” EX1033, 1; EX1032, 1; EX1034, 1; EX1035, 1; EX1049, ¶35.

4. COLCOT Trial Data

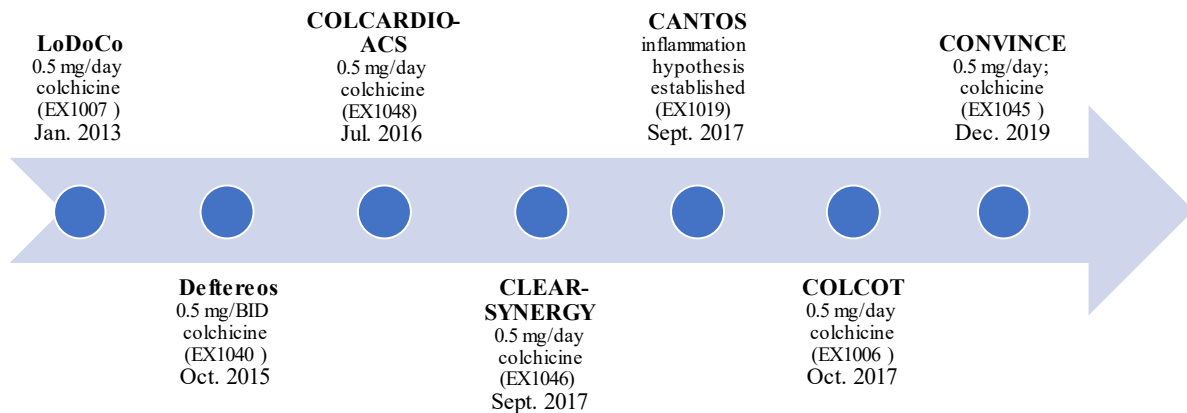
Before the '063 patent's November 13, 2020, filing date, Tardif 2019 reported COLCOT's results, which, as explained by Dr. Ridker, confirmed the earlier findings of LoDoCo. EX1022, 5-8; EX1049, ¶¶54-56.

Also before November 13, 2020, Bouabdallaoui published the '063 patent's same *post hoc* COLCOT analysis based on “the usual journey of patients with MI” for the time-to-treatment-initiation (TTI) cutoff lines of days 0 to 3 (“in-hospital management”), days 4 to 7 (“early post-discharge period”), and days 8 to 30 (“late post-discharge period”). EX1005, 3, 4-5, Table 3; *see also* EX1025, 36; EX1049, ¶¶57-58. Bouabdallaoui states that the *post hoc* TTI data show that initiating low-dose colchicine within 3 days after MI “is associated with a reduction of 48% in the risk of the primary endpoint” which “support[s] the strategy of in-hospital initiation of colchicine.” EX1005, 5. Bouabdallaoui, however, does not demonstrate any statistically significant difference in outcomes between different TTI intervals. EX1049, ¶¶58-59.

5. Additional Colchicine Evaluations and Studies

By 2019, there was significant momentum reflected in multiple studies toward using low-dose colchicine for atherosclerotic conditions, with a trend of early

treatment initiation. EX1040, 2 (Deftereos safely initiating treatment “≤12 hours from the onset of chest pain”); EX1046, 2, 3; EX1047, 6; EX1048, 2; EX1045, 1; EX1038, ¶¶36-37, 38-39, 40; EX1049 ¶¶49-53.



For example, multiple reports reflect motivation to initiate daily low-dose colchicine treatment early post-MI to reduce the risk of subsequent cardiovascular events. *See* EX1030, 1, 10 (meta-analysis finding that “colchicine reduces the composite cardiovascular outcome by approximately 60%”); EX1043, 2 (colchicine showed “an overall benefit on cardiovascular risk reduction”); EX1029, 2 (“[t]here is increasing evidence supporting a potentially beneficial role for colchicine therapy in prevention of cardiovascular disease (CVD)”); EX1026, 4 (the LoDoCo trial “strongly suggest[ed] a marked benefit” of low-dose colchicine and that the “use of

low-dose colchicine is now being explored in trials totalling 15000 patients” including LoDoCo2 trial and the COLCOT trial); EX1044, 4 (“Colchicine could be a safe and effective inhibitor of the inflammation cascade induced by extracranial or intracranial atherosclerosis, providing thus an additional therapeutic agent in secondary noncardioembolic stroke prevention.”); EX1049, ¶¶43-53.

C. Post-MI Secondary Prevention Treatment

As Dr. Ridker explains, long before 2019, it had been common practice to initiate proven secondary prevention treatment for MI survivors as soon as practical, more specifically, prior to hospitalization discharge and typically no more than 3-day post-MI, to provide long-term cardiovascular risk reduction benefit. EX1049, ¶¶60-63; EX1014, 1; EX1011, 1; EX1009, 13, 24.

Early treatment initiation is specifically recommended in ESC Guidelines (EX1009). *See infra* §II.D.4. Consistent with such recommendation, Stenestrand showed clinical benefits associated with early initiation of statin treatment in MI patients before or at patient discharge, such as reduced 1-year mortality, and concludes that “our findings suggest that initiation of statin treatment before or at the time of hospital discharge should be recommended for AMI survivors” “for statin treatment as secondary prevention.” EX1008, 4, 5, 6; EX1049, ¶¶60-63.

D. Asserted Ground References

1. COLCRYS Package Insert (“COLCRYS,” EX1016)

COLCRYS, prescription information for COLCRYS™ (colchicine, USP) tablets, is a webpage published and downloadable from the FDA website and had been publicly accessible at least as of August 24, 2009. EX1016, 1; EX1038, ¶¶30-32; EX1049, ¶85. COLCRYS is prior art under 35 U.S.C. § 102(a)(1).

COLCRYS discloses that COLCRYS™ was approved for treating gout flares and FMF and “supplied for oral administration as purple, film-coated, capsule-shaped tablets” that contain a low dose of active ingredient colchicine USP (0.6 mg). EX1016, 1, 9.

2. US 10,206,891 (“Nidorf,” EX1007)

U.S. Patent No. 10,206,891 (“Nidorf”) issued November 16, 2017, based on PCT/AU2013/001261, filed on November 1, 2013, and is prior art under 35 U.S.C. §§ 102(a)(1) and (a)(2). EX1007, 1; EX1048, ¶64.

Nidorf describes the LoDoCo trial that administered 0.5 mg/day of colchicine to patients with “angiographically proven coronary disease” clinically stable for at least 6 months, including patients with past MI. EX1007, 17:66-18:8, 18:31-34, 20:3-5 (teaching LoDoCo primary analysis was stratified by, *inter alia*, diagnosis of “past myocardial infarction”); EX1020, Table 1 (confirming that 23% of the enrolled patients in LoDoCo had “past AMI [acute myocardial infarction] or UA”); EX1049,

¶¶65-67. Nidorf further teaches that the LoDoCo enrolled patients treated with aspirin or statins. EX1007, 20:3-7 (“the primary analysis was also stratified by... therapy with *aspirin*..., high dose *statin* therapy”).

Nidorf discloses that LoDoCo achieved its primary efficacy outcomes and demonstrates that the addition of colchicine 0.5 mg/day to standard therapy in patients with stable coronary disease significantly reduces the risk of a cardiovascular event, including an ACS [acute coronary syndrome], out of hospital cardiac arrest and non-cardio-embolic ischemic stroke and that “[t]he effect of colchicine on the primary outcome was evident early and the benefits of colchicine continued to accrue throughout the follow up period.” EX1007, 19:26-29; 19:6-14, 20:34-36, 21:55-59; EX1049, ¶¶68-69.

3. COLCOT Protocol (EX1006)

COLCOT Protocol is an updated version of the original September 16, 2015 COLCOT trial (Study No. NCT02551094) protocol, published on the clinicaltrial.gov website on March 8, 2017. EX1006, 1. As Dr. Ridker explains, Clinicaltrial.gov is a well-known resource routinely posting newly submitted clinical trials in a timely manner, used by skilled cardiologists to check updated clinical study information. EX1049, ¶76, n.103. As Mr. Cruitt further explains, the webpage of the March 8, 2017, version of the updated COLCOT Protocol was accessible to

the public at least as of October 20, 2017. EX1038, ¶¶23-25. Thus, COLCOT Protocol is prior art to all challenged claims under 35 U.S.C. § 102(a)(1).

COLCOT Protocol describes the prior knowledge that “[a]therosclerosis is the most common cause of myocardial infarction” and that “inflammation plays a key role in the initiation, progression and manifestations of atherosclerosis” and is likely “responsible for the high rate of cardiovascular events.” EX1006, 4; EX1049, ¶77. COLCOT Protocol further recognizes that “[c]onsiderable work,” including LoDoCo, “has highlighted the potential of colchicine in the treatment of cardiovascular diseases mediated by pro-inflammatory processes.” EX1006, 4; EX1049, ¶77.

COLCOT Protocol describes the same COLCOT trial as the ’063 patent, explaining that the study evaluates colchicine’s reduction of cardiovascular event rates in “[p]atients who have suffered a documented acute myocardial infarction within the last 30 days,” but “after having completed any planned percutaneous revascularization procedures associated with their initial infarction” and only if the patient does not have poorly controlled medical condition, current cardiogenic shock, or hemodynamic instability. *Compare* EX1006, 1, 5 *with* EX1001, 1:66-2:28, 7:22-8:40; EX1049, ¶78. COLCOT Protocol describes administering a 0.5 mg tablet of colchicine once per day and the same cardiovascular event primary outcome

measures as those recited in the '063 patent claims. EX1006, 1, 2, 4; EX1049, ¶¶78-79.

4. ESC Guidelines (EX1009)

The “2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation” (“ESC Guidelines”) were published online on August 26, 2017. EX1009, 1. As Dr. Ridker explains, ESC Guidelines were compiled by the European Society of Cardiology (ESC), a well-respected professional association routinely providing guidance and recommendations to skilled cardiologists. EX1049, ¶80, n. 110. Since its online publication, ESC Guidelines had been publicly available to skilled cardiologists, and by 2018, they had been reviewed and cited by clinicians around the world. EX1049, ¶80, n. 112; EX1023, 8 (Ref. No. 2); EX1024, 1, 20 (Ref. No. 20). As Mr. Cruitt confirms, the online version of ESC Guidelines had been accessed publicly as of September 4, 2017. EX1038, ¶¶26-28. Thus, ESC Guidelines are prior art to all challenged claims under 35 U.S.C. § 102(a)(1).

ESC Guidelines “summarize and evaluate available evidence with the aim of assisting health professionals in selecting the best management strategies for” STMI patients. EX1009, 5. ESC Guidelines also acknowledge that “low-risk patients with successful primary PCI and complete revascularization can safely be discharged from hospital on day 2 or day 3 after PCI” and that once discharged from the hospital,

“[l]ow treatment adherence” and “[d]elayed outpatient follow-up” result in worse clinical outcomes. EX1009, 24, 30; EX1049, ¶¶81-84. To achieve “increase[d] patient adherence after discharge” and “early and sustained clinical benefits,” ESC Guidelines recommend that once passing the urgent care period (usually the first 12 hours), long-term secondary prevention statin treatments “should be started as early as possible.” EX1009, 33; EX1049, ¶84.

5. Bouabdallaoui (EX1005)

Bouabdallaoui was published online on August 29, 2020, ahead of the subsequent print in the European Heart Journal. EX1005, 1. As Dr. Ridker explains, the data in Bouabdallaoui had been presented to cardiologists like himself during the European Society of Cardiology’s August 29-September 1, 2020, “ESC Congress 2020,” and he became aware of Bouabdallaoui when the online version became available around the same time. EX1049, ¶¶70-71; EX1025, 36. Because at least claims 1-26, 28, and 40-50 are not entitled to any priority date before the actual filing date of November 13, 2020, Bouabdallaoui is prior art to those claims under 35 U.S.C. § 102(a)(1). *Infra* § III.C.

Bouabdallaoui discloses the same TTI *post hoc* analysis of COLCOT as the ’063 patent and concludes that the results “support[] the strategy of in-hospital initiation of colchicine in order to improve CV outcomes post-MI.” *Compare*

EX1005, 4, 5, Table 3 and Figure 2 *with* EX1001, 11:26-33 and 12:24-33, Table 3 and Figure 2; EX1049, ¶¶72-75.

III. THE '063 PATENT

A. The Challenged Claims

The '063 patent has three independent claims, claims 1, 8, and 27.

- Claim 1 recites a method of treating MI patients that previously received PCI by administering colchicine at a daily low dose without a preloading dose within about 3 days of the MI.
- Claim 8 similarly recites a method of treating MI patients by administering colchicine at a daily low dose without a preloading dose within about 3 days of the MI to reduce one of the recited cardiovascular events.
- Claim 27 recites a method of reducing stroke risk in MI patients by initiating colchicine administration with a daily low dose within 30 days of the MI.

EX1049, ¶¶86, 88.

The dependent claims further recite:

- Additional medication claims (2-5, 28-32, 40-43): the patient “was prescribed” a medication or more specifically an antiplatelet agent, aspirin, or a statin. These “was prescribed” claims do not require concurrent or combination treatment. *See* EX1001, 4:20-22 (“previously prescribed” embodiment), 4:23-25 (separately describing “concurrent[.]” embodiment).

- Cardiovascular event claims (6, 7, 9-11, 50): the patient is at a lower risk of a cardiovascular event or more specifically an ischemic cardiovascular event, relative to a patient not being administered colchicine (claims 6 and 7); the cardiovascular event of claim 8 is myocardial infarction (claim 9), stroke (claim 10), urgent hospitalization for angina requiring coronary revascularization (claim 11), or resuscitated cardiac arrest (claim 50).
- Patient population claims (12, 26, 33, 39, 44, 49): the patient has atherosclerotic coronary artery disease (claims 12, 33, and 44) or is an adult human (claims 26, 39, and 49).
- “Initiation upon assessment” claims (13, 26, 46): the administration of colchicine is initiated upon assessment in (a) an emergency department (ED), (b) the hospital, or (c) a medical office setting.
- Tablet claims (14-16, 37, 38, 47, 48): the colchicine is a tablet, or more specifically a coated tablet, or more specifically a film-coated tablet.
- Dose and frequency claims (17-25, 35, 45): the colchicine is administered at more specific doses, including 0.3 to 0.7 mg, 0.4 to 0.6 mg, or 0.5 mg, or more specific dosing frequencies, including once to three times a day, or more specifically once a day.
- Administration initiation time claim (28): administering colchicine within 4 to 7 days of the MI.

EX1049, ¶¶87, 88.

B. Prosecution of the '063 Patent

The '063 Patent issued from Application No. 17/097,285 (Nov. 13, 2020), which claims priority to provisional application Nos. 63/093,988 (Oct. 20, 2020) and 62/935,865 (Nov. 15, 2019). EX1001, (60). As further discussed in Section III.C, the claims reciting administering to patients “within about 3 days” and “within 4 to 7 days” after MI are *not* entitled to an effective filing date earlier than November 13, 2020.

As-filed claim 1 recited:

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.

EX1002, 5. As-filed dependent claim 2 further recited “wherein percutaneous coronary intervention was performed for treating the patient’s MI,” and as-filed dependent claims 9-12 further recited reducing individual cardiovascular events, including resuscitated cardiac arrest, myocardial infarction, stroke, or urgent hospitalization for angina requiring coronary revascularization. *Id.* While the Examiner rejected as-filed claim 1 as anticipated by Hennessy (EX1028), he determined that claims 2 (PCI claim), 9 (resuscitated cardiac arrest claim), 11 (stroke claim), and 12 (angina claim) would be allowable if rewritten in an independent form. EX1002, 295, 298. After Applicant amended claim 1 to add the “without preloading

dose” and the PCI limitations and amended claim 9 into an independent claim that incorporated the cardiovascular events separately recited in as-filed claims 9, 11 and 12 (*id.*, 328, 345-48, 353, 383), the Examiner allowed those claims, finding these amendments overcame Hennessy, his selected closest prior art. *Id.*, 396-97.

The Examiner further distinguished the allowed claims from Deftereos, “Circulation (2015), 132(15), pp. 1395-1403,” (EX1040, “Deftereos”) which he understood to disclose all claim 1 limitations except the “without preloading dose” limitation but found “no motivation to delete the loading dose of [Deftereos] and treat these patients by the method of [Hennessy].” EX1002, 397.

In sum, the Examiner allowed the claims based on the following understanding: (1) Hennessy was the closest prior art; (2) Hennessy did not disclose performing PCI on MI patients or reducing the cardiovascular events recited in the claims; and (3) there was no motivation to remove Deftereos’s preloading dose.

C. At Least Claims 1-26, 28, and 40-50 Are Not Entitled to an Effective Filing Date Earlier than November 13, 2020

Claims 1-26, 28, and 40-50 require administering colchicine “within about 3 days of the MI” (claims 1-26 and 40-50) or “within 4 to 7 days of the MI” (claim 28). These limitations are not described in the November 15, 2019, or October 20, 2020 provisional applications. *See generally* EX1003; EX1004; EX1049, ¶¶90-96. To the contrary, both provisional applications describe the COLCOT trial protocol

of initiating treatment within 30 days of an MI without disclosing the claimed initiation periods, with the November 15, 2019 provisional application emphasizing that COLCOT “[p]atients were enrolled a mean of 13.5 days after myocardial infarction.” EX1004, 9:2; EX1049, ¶¶93-94.

These claims are thus not entitled to an effective filing date earlier than the November 13, 2020, nonprovisional application. *Dynamic Drinkware, LLC v. Nat’l Graphics, Inc.*, 800 F.3d 1375, 1379-80 (Fed. Cir. 2015).

D. EPO Novelty Rejection and Abandonment

Similar to claim 27 of the ’063 patent, Patent Owner’s EP3821889A application claim 1 recited:

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.

EX1037, 30. Citing, *inter alia*, prior art reporting LoDoCo results, the European search opinion found that “the subject-matter of claims 1-15 is not new within the meaning of Article 54(1) and (2) EPC.” *Id.*, 45-46. Patent Owner failed to respond, and the application was held withdrawn. *Id.*, 59.

IV. LEVEL OF ORDINARY SKILL IN THE ART

The '063 patent involves treating post-MI patients with colchicine. Based on this context, a person of ordinary skill in the art (“POSA”), which Dr. Ridker also refers to as a “skilled cardiologist,” would have:

- An M.D. degree and be board-certified with a subspecialty in the treatment of cardiovascular disease.
- At least 3-5 years of experience, following board certification, in cardiology and cardiovascular disease treatment and sufficient clinical experience to understand standard good medical practice in patient management.
- Been familiar with acute coronary syndromes, stable coronary diseases, cardiovascular diseases, and their standard treatments, including the acute management and long-term secondary preventions of myocardial infarction.
- Been aware of research relating to cardiovascular disease progression, including the role of inflammatory pathways in secondary cardiovascular events.

EX1049, ¶89.

V. CLAIM CONSTRUCTION

A. “Treating” Preamble (Claims 1-26, 40-50)

The preamble of claims 1-26 and 40-50 recite “a method of treating a patient after having a myocardial infarction (MI).” EX1001, claims 1-26, 40-50. The intrinsic evidence supports construing the preamble to mean exactly what it says: *a*

method of treating a patient after having a MI without requiring any type or degree of clinical efficacy. In re Montgomery, 677 F.3d 1375, 1380 (Fed. Cir. 2012) (“We are skeptical that a proper interpretation of [the claim term ‘for the treatment or prevention of stroke or its recurrence’] would include an efficacy requirement”).

First, in context, claim 1 merely recites “treating” without specifying any clinical outcome or any “therapeutically effective amount” of colchicine. That is, the claim language does not require clinical efficacy. EX1049, ¶101.

Second, the specification does not define “treating” as requiring any clinical efficacy or otherwise teaches that this term requires any actual treatment. EX1049, ¶¶103, 104. The specification also refers to patients who are “concurrently ***being treated with*** a medication (for example, antiplatelet agent, a statin, aspirin, or a combination thereof),” further supporting construing “treat” as “providing treatment to.” EX1001, 4:23-25.

Third, in its ordinary meaning to a POSA, “treat” or “treating” includes providing care to a patient by, for instance, prescribing or administering medication with the objective of managing a medical condition, but not necessarily achieving efficacy. EX1049, ¶¶97-103. Consistent with this understanding, COLCOT Protocol also mentions “treatment” in the context of evaluating potential clinical effects. EX1006, 1 (“***evaluat[ing] whether long-term treatment*** with colchicine reduces

rates of cardiovascular events in patients after myocardial infarction.”); EX1049, ¶103.

B. “Reducing the Risk of a Stroke” Preamble (Claims 27-39)

The preamble “reducing the risk of a stroke” is an intended result, not entitled to patentable weight. EX1049, ¶¶104-108; *Bristol-Myers Squibb Co. v. Ben Venue Lab’ys, Inc.*, 246 F.3d 1368, 1375-76 (Fed. Cir. 2001) (finding preamble language “a method for treating a cancer patient to effect regression of a taxol-sensitive tumor, said method being associated with reduced hematologic toxicity” “is only a statement of purpose and intended result”). As in *Bristol-Myers Squibb*, here, “reducing the risk of a stroke” does “not result in a manipulative difference in the steps of the claim” and is non-limiting. *Bristol-Myers Squibb*, 246 F.3d at 1376. Nor does the “reducing the risk of a stroke” provide an antecedent basis for affirmative limitations in these claims. EX1001, claims 27-39.

C. “Wherein the Patient Is at a Lower Risk of a Cardiovascular Event” (claims 8-11, 20-23)

Like the claims 27-39 preamble, the 8[e] “wherein” clause “is only a statement of purpose and intended result” that “does not result in a manipulative difference in the steps of the claim” and is thus a non-limiting intended result and does not add patentable weight to the claims. *Bristol-Myers Squibb*, 246 F.3d at 1376; *see also Syntex (U.S.A.) LLC v. Apotex, Inc.*, 407 F.3d 1371, 1378 (Fed. Cir. 2005) (finding a clause that “simply describes the intended result” of following the steps in claimed

method was not limiting); *Minton v. Nat’l Ass’n of Sec. Dealers, Inc.*, 336 F.3d 1373, 1381 (Fed. Cir. 2003) (“[a] whereby [or wherein] clause in a method claim is not given weight when it simply expresses the intended result of a process step positively recited.”).

VI. STATEMENT OF PRECISE RELIEF REQUESTED

Pursuant to 37 C.F.R. §§ 42.104(b) and 42.22(a)(1), Petitioner requests review and cancellation of claims 1-50 of the ’063 patent pursuant to the following challenges:

Ground	Claims	Basis	References
1	1-13, 17-26, 28, 40-46, 49, 50	§ 102	Bouabdallaoui
2	27, 29-36, 39	§ 102	COLCOT Protocol
3	1-50	§ 103	Nidorf in view of COLCOT Protocol, ESC Guidelines, and COLCRYS
4	1-26, 28, 40-50	§ 103	Bouabdallaoui in view of COLCRYS

VII. ANTICIPATION OF CHALLENGED CLAIMS

A. Ground 1: Claims 1-13, 17-26, 28, 40-46, 49, and 50 Are Anticipated by Bouabdallaoui

As explained in Section III.C, Bouabdallaoui is prior art to claims 1-13, 17-26, 28, 40-46, 49, and 50 and discloses the same COLCOT *post hoc* analysis relied upon in the ’063 patent to support these claims. *Compare* EX1005 *with* EX1001, Example

1. Unsurprisingly, as shown below, Bouabdallaoui anticipates these claims.²
EX1049, ¶109.

1. Independent Claims 1 and 8

Ground 1 Chart

Claim limitations	Bouabdallaoui
1[a], 8[a]:	Bouabdallaoui discloses that “COLCOT was an international multicentre, randomized, double-blinded trial that randomly assigned patients to receive either low-dose colchicine (0.5mg once daily) or placebo.... Patients were considered eligible if they had a recent MI (<30 days)” EX1005, 2-3. A POSA would understand that the disclosed patient eligibility criteria teach treating post-MI patients. EX1049, ¶109.
1[b], 8[b]:	Bouabdallaoui discloses that “COLCOT was an... trial that randomly assigned patients to receive either low-dose colchicine (0.5mg once daily) or placebo.” EX1005, 2-3. Bouabdallaoui further discloses that “<i>[c]olchicine at the low dose of 0.5mg daily</i> was shown to significantly reduce the risk of ischaemic CV events by 23% compared with placebo when

² As shown in Ground 4, Bouabdallaoui in view of COLCRYST further renders obvious all claims not entitled to an effective filing date earlier than November 13, 2020.

	initiated within the first 30 days after MI in the Colchicine Cardiovascular Outcomes Trial (COLCOT).” <i>Id.</i>, 2. A POSA would understand that the 0.5 mg once-daily dose disclosed in Bouabdallaoui meets limitations 1[b] and 8[b]. EX1049, ¶109.
1[c], 8[c]:	<i>See</i> limitation 1[b]. A POSA would understand that Bouabdallaoui’s disclosure of administering 0.5 mg colchicine once daily is a complete dosing protocol and excludes the possibility of adding a higher preloading dose. EX1049, ¶109.
1[d], 8[d]:	Bouabdallaoui discloses that 26.0% of the colchicine-treated patients initiated treatment 0-3 days of the MI. EX1005, Table 1. Bouabdallaoui discloses that “primary endpoint event occurred in 4.3% of patients in the colchicine group, as compared with 8.3% of those in the placebo group when TTI was between Days 0 and 3.” <i>Id.</i>, 4. A POSA would understand that Bouabdallaoui’s disclosures of patients with TTI of 0-3 days and their efficacy results teach limitations 1[d] and 8[d]. EX1049, ¶109.

1[e]	Bouabdallaoui discloses that “[a]ll patients enrolled in the trial benefitted from percutaneous coronary intervention whenever indicated and guidelines-directed management of CV disease prior to randomization.” EX1005, 3. A POSA would understand that Bouabdallaoui’s descriptions above teach that PCI was performed on the enrolled MI patients. EX1049, ¶109.
8[e]	Bouabdallaoui discloses that “[t]his analysis of COLCOT shows that early initiation of low-dose colchicine within the first 3 days after MI is associated with a reduction of 48% in the risk of the primary endpoint consisting of a composite of CV death, resuscitated cardiac arrest, MI, stroke, or urgent hospitalization for angina requiring coronary revascularization, in comparison with placebo.” EX1005, 5. A POSA would understand that Bouabdallaoui’s descriptions of reducing the risks of primary endpoints match the recited lower cardiovascular event risks and meets limitation 8[e]. EX1049, ¶109.

2. Additional medication claims 2-5, 40-43

Claims 2-5 and 40-43 are anticipated by Bouabdallaoui’s disclosures that nearly all enrolled patients had been treated with aspirin and statins. EX1005, 3-4 (“[b]ackground therapy included aspirin, a second anti-platelet agent and a statin in

98.8%, 98.0%, and 99.0% of patients, respectively”), Table 1; EX1049, ¶¶110-111; § III.A, *supra*.

3. Cardiovascular event claims 6-7, 9-11, 28, and 50

Claims 6-7, 9-11, and 50 are anticipated by Bouabdallaoui’s disclosure that colchicine, initiated within 3 days post-MI, reduced risks of the recited cardiovascular events, and claim 28 is anticipated by Bouabdallaoui’s disclosure that colchicine, initiated within 4-7 days post-MI, reduced the stroke incidence.³ EX1005, 4, 7, Table 3; EX1049, ¶¶112-115; § III.A, *supra*.

4. Patient population claims 12, 26, 44, and 49

Claims 12 and 44, reciting that the patient has atherosclerotic coronary artery disease, are anticipated by Bouabdallaoui’s disclosures of treating MI patients where “[m]yocardial infarction (MI) is associated with an acute exacerbation of cardiovascular (CV) inflammation superimposed on the *chronic atherosclerosis-related* inflammatory process.” EX1005, 2; EX1049, ¶¶116-118; § III.A, *supra*. As Dr. Ridker explains, such disclosures of treating MI patients with atherosclerotic conditions are consistent with prior knowledge that “[a]therosclerosis is the most

³ The Bouabdallaoui’s 4-7 day stroke data is not reported as statistically significant. EX1005, 4; EX1049, ¶114. As addressed in Section V.B, however, claim 28 does not require actual—let alone statistically significant—stroke reduction.

common cause of myocardial infarction.” EX1006, 4; EX1015, 1; EX1049, ¶117. Bouabdallaoui’s disclosures that “[p]atients were mostly men (81.0%) with a mean age of 60.5 years” anticipate the “treating adult human patient” limitations of claims 26 and 49. EX1005, 3; EX1049, ¶118.

5. “Initiation upon assessment” claims 13, 46

These claims are anticipated by Bouabdallaoui’s disclosures that its “results support *in-hospital initiation* of adjunctive anti-inflammatory therapy with colchicine for post-MI prevention” and that TTI days 0-3 “refer to in-hospital management.” EX1005, 2, 3, 5, 7; EX1048, ¶¶119-121; § III.A, *supra*. As Dr. Ridker explains, these teachings show that the administration of colchicine in patients within 0 to 3 days of the MI was initiated after the patients were assessed for eligibility and before they were discharged from the hospital. EX1049, ¶121.

6. Dose and frequency claims 17-25, 45

These claims, which all cover administering 0.5 mg colchicine once daily, are anticipated by Bouabdallaoui’s disclosures that the COLCOT trial patients received “low-dose colchicine (0.5mg once daily).” EX1005, 2, 3; EX1049, ¶122; § III.A, *supra*.

B. Ground 2: Claims 27, 29-36, and 39 Are Anticipated by COLCOT Protocol

Claim 27 recites a single step method of “initiating the administration of colchicine at a daily low dose to the patient within about 30 days of an MI” based

on the COLCOT trial described in Example 2 of the '063 patent. EX1001, claim 27, Example 2. The protocol for Example 2, however, had been published in the prior art COLCOT Protocol, which identically discloses this method and expressly or inherently discloses every limitation of claim 27 and its dependent claims 29-36 and 39. As shown below, these claims are anticipated by COLCOT Protocol.⁴ EX1049, ¶¶123-126.

1. Independent Claim 27

Ground 2 Chart

Claim limitations	COLCOT Protocol
27[a]	Preamble is non-limiting. <i>See</i> § V.B, <i>supra</i>. The preamble is also inherently anticipated by COLCOT Protocol's disclosures that COLCOT "evaluates whether long-term treatment with colchicine reduces rates of cardiovascular events in patients after myocardial infarction," which includes reducing the rate of "stroke." EX1006, 1, 2-3; EX1049, ¶¶126-132.

⁴ As shown in Ground 3, all of the '063 patent claims are also obvious based on the combination of COLCOT Protocol and other related prior art references.

27[b]	COLCOT Protocol discloses that the enrolled patients will receive “colchicine (0.5 mg per day).” EX1006, 1. A POSA would understand that COLCOT Protocol’s 0.5 mg once-daily dose meets limitation 27[b]. EX1049, ¶126.
27[c]	COLCOT Protocol discloses that the COLCOT study treats “[p]atients who have suffered a documented acute myocardial infarction within the last 30 days” and that enrolled patients “must have suffered a documented acute myocardial infarction within the last 30 days.” EX1006, 1, 2, 5. A POSA would understand that these disclosures teach limitation 27[c]. EX1049, ¶126.

As shown, COLCOT Protocol expressly teaches initiating colchicine treatment at a daily low dose (0.5 mg/day) within 30 days of an MI, as recited in limitations 27[b]-[c]. Because preamble 27[a] is non-limiting (*see supra* § V.B), COLCOT Protocol thus identically teaches and anticipates the method of claim 27, even without provided data for “reducing the risk of a stroke,” as recited in the preamble.

Even if the “reducing the risk of a stroke” preamble is limiting, the ’063 patent admits that the method of administration according to COLCOT Protocol inherently reduces the risk of a stroke:

- “Colchicine at a daily low dose of 0.5 mg led to a statistically significant lower risk of ischemic cardiovascular events.... This reduction... was particularly prominent... in the reduction... stroke....” EX1001, 2:7-23.
- “In COLCOT, the risk of the primary composite efficacy end point of ... stroke... was significantly lower among the patients who were randomly assigned to receive 0.5 mg of colchicine once daily” EX1001, 39:11-20.

Thus, “efficacy is inherent in carrying out the claim steps” of administering daily low doses (e.g., 0.5 mg/day) of colchicine to the patient within about 30 days of an MI. *In re Montgomery*, 677 F.3d at 1381 (holding that the clinical protocol for administering ramipril to stroke-prone patients inherently anticipates the stroke treatment claims at issue because administering ramipril inevitably treats or prevents stroke); *In re Huai-Hung Kao*, 639 F.3d 1057, 1070 (Fed. Cir. 2011) (affirming Board’s finding claimed “food effect” inherent based on the applicant’s specification); EX1049, ¶¶126-132.

2. Additional medication claims 29-32

COLCOT Protocol expressly teaches that enrolled patients “must be treated according to the national guidelines (including *antiplatelet therapy, statin....*),” meeting the additional limitations recited in claims 29, 30, and 32. *See* EX1006, 5; EX1049, ¶¶133-134; § III.A, *supra*.

Regarding the claim 31 “aspirin” limitation, a POSA would have immediately envisaged aspirin—the most common cardiovascular antiplatelet therapy as of 2019—from COLCOT Protocol’s disclosure of “antiplatelet therapy” according to “national guidelines.” EX1049, ¶135; *see, e.g.*, EX1021, 3; EX1009, 31; *Kennametal, Inc. v. Ingersoll Cutting Tool Co.*, 780 F.3d 1376, 1381 (Fed. Cir. 2015) (“a reference can anticipate... if a person of skill in the art, reading the reference, would ‘at once envisage’ the claimed arrangement or combination”) (internal citation omitted); *Arthrocare Corp. v. Smith & Nephew, Inc.*, 406 F.3d 1365, 1373 (Fed. Cir. 2005) (finding anticipation based on a POSA’s prior knowledge).

3. Patient population claims 33, 39

A POSA would understand that COLCOT Protocol’s disclosure that “[a]therosclerosis is the most common cause of myocardial infarction, stroke and peripheral arterial disease” (EX1006, 1, 4) teaches treating an MI patient having atherosclerotic coronary artery disease, as required by claim 33. EX1049, ¶136. Similarly, its “[m]ales and females of at least 18 years of age” inclusion criteria (EX1006, 5) teaches treating adult human patients, as recited in claim 39. EX1049, ¶137.

4. Dose and frequency claims 34, 35

As shown in Ground 2 Chart element 27[b], COLCOT Protocol expressly teaches the 0.5 mg and “once per day” limitations of claims 34 and 35. EX1049, ¶138.

5. “Initiation upon assessment” claims 36

Anticipating claim 36, COLCOT Protocol (1) teaches the location of COLCOT is the Montreal Heart Institute (a hospital facility), and (2) requires an initial assessment by the investigator (all medical doctors) to determine if the patient is a suitable candidate, which a POSA would have understood to occur at a hospital (the study site), ER, or medical office. EX1006, 7; EX1049, ¶139.

VIII. OBVIOUSNESS OF ALL CHALLENGED CLAIMS

A. Ground 3: Claims 1-50 Would Have Been Obvious over Nidorf in View of COLCOT Protocol, ESC Guidelines, and COLCRYS

All claims would have been obvious over the Ground 3 references commonly relating to colchicine and/or initiating secondary preventive therapy in post-MI coronary artery disease patients:

- Nidorf (EX1007) and COLCOT Protocol (EX1006) teaches administering 0.5 mg colchicine daily to post-MI patients with stabilized coronary disease for secondary prevention,

- ESC Guidelines (EX1009) recommend earlier initiation of secondary preventive therapy for stabilized patients before hospital discharge, typically around 2-3 days post-MI, and
- COLCRYS describes commercially available film-coated colchicine tablets. EX1049, ¶¶37, 39, 140, 143-146.

A POSA would have been motivated to combine these teachings to shorten LoDoCo's (Nidorf) colchicine initiation time to within COLCOT Protocol's 30 days post-MI window, especially at around 2-3 days post-MI, to maximize the treatment benefits. *Id.*, ¶¶141, 147-151. A POSA would have had a reasonable expectation of success in reducing the risk of secondary cardiovascular events, such as stroke, in view of colchicine's demonstrated efficacy in LoDoCo at longer initiation times and proof from CANTOS that targeting the inflammatory pathway inhibited by colchicine as soon as 30 days post-MI reduced cardiovascular events in those patients. *Id.*, ¶¶151-152.

For claims 1-26, 28, and 40-50 that are not entitled to an effective filing date earlier than November 13, 2020, the motivation and expectation of success are reinforced and confirmed by the reported success according to Tardif 2019 and Bouabdallaoui in reducing cardiovascular events by initiating colchicine treatment within 30 days post-MI, including within 0-3 days. *Id.*, ¶153; § III.C, *supra*.

1. Independent Claims 1, 8, and 27

a. Claims 1 and 8

i. Nidorf and COLCOT Protocol Teach All Limitations Except “Within About 3 Days of the MI”

First, Nidorf’s LoDoCo trial teaches limitations 1[a] and 8[a], describing administering colchicine as secondary preventative therapy for “patients with objectively diagnosed and clinically stable coronary disease,” including patients who had an MI. EX1007, 17:60-18:8, 18:31-34, 20:25-21:65, 20:3-5 (teaching that primary analysis was stratified by, *inter alia*, diagnosis of “past myocardial infarction”); EX1020, Table 1 (confirming that 23% of the LoDoCo colchicine-treated patients had prior MI or unstable angina); EX1049, ¶¶143-144, 155-156. Although Nidorf does not specify the number of post-MI patients treated in LoDoCo, treating such patients is at least obvious from its patient stratification criteria. EX1007, 20:3-5; EX1049, ¶¶68, 145-146; *Grünenthal GmbH v. Antecip Bioventures II LLC*, PGR2019-00003, Paper 22 at 31 (PTAB May 5, 2020) (claims obvious where the prior art disclosed “inclusion criteria for patients to be included in the study, and that patient population overlap[ped] the patient population set forth in the claims”). COLCOT Protocol also teaches initiating colchicine treatment within 30 days post-MI. EX1006, 1 (targeting “patients after myocardial infarction”); EX1049, ¶¶78, 146.

Second, Nidorf's disclosure that LoDoCo administered 0.5 mg/daily colchicine without a preloading dose meets limitations 1[b], 1[c], 8[b], and 8[c]. EX1007, 18:18-24; EX1049, ¶143. COLCOT Protocol similarly discloses administering 0.5 mg/daily colchicine without a preloading dose. EX1006, 2; EX1049, ¶146.

Third, regarding the PCI limitation (1[e]), Nidorf discloses that LoDoCo's primary analysis was stratified by baseline characteristics including "coronary angioplasty," which a POSA would understand refers to, and renders obvious treating, patients who had PCI prior to colchicine administration. EX1007, 19:48-51, 20:3-5 (analysis stratified by coronary angioplasty); *see also* EX1020, 12-13, Table 1 (percutaneous coronary angioplasty (PTCA)); EX1049 ¶23. COLCOT Protocol further teaches limitation 1[e] by disclosing treating patients "after having completed any planned percutaneous revascularization procedures associated with their initial infarction" and that the "[p]atient must have completed any planned percutaneous revascularization procedures associated with his or her qualifying myocardial infarction." EX1006, 2, 5; EX1049, ¶78.

Fourth, to the extent Patent Owner argues that the 8[e] "wherein" clause is limiting, Nidorf teaches reducing risks of all of the recited 8[e] cardiovascular events, reporting that LoDoCo "significantly reduces the risk of a cardiovascular event, including an ACS, out of hospital cardiac arrest and non-cardio-embolic ischemic

stroke” and that “[t]he effect of adding colchicine became evident early, continued to accrue over time.” EX1007, 18:31-34, 18:65-67, 19:55-59, 19:63-64; EX1049, ¶¶28, 69, 143. Nidorf further teaches that “ACS” includes an acute myocardial infarction or unstable angina. EX1007, 19:6-14; EX1049, ¶¶39, 68.

Thus, Nidorf and COLCOT Protocol each teach all limitations of claims 1 and 8, except specifically teaching initiating treatment “within about 3 days of the MI.” Based on what was known as of 2019, it would have been obvious to initiate low-dose colchicine treatment at around day 2 or 3 post-MI.

ii. Motivation to Initiate Treatment “Within About 3 Days of the MI”

A POSA would have understood and been motivated to shorten Nidorf’s treatment initiation time to around 2-3 days post-MI both (1) by routine optimization within COLCOT Protocol’s 30-day window, and (2) in view of ESC Guidelines’ teachings, the common practice for improved patient compliance and earlier, long-term therapeutic benefit, and the growing clinical trial trend. EX1049, ¶¶141, 145, 147-154, 157-165.

First, the claimed “within about 3 days of the MI” would have been a matter of routine optimization within COLCOT Protocol’s 30-day window. EX1006, 1, 5; EX1049, ¶147; *Galderma Lab ’ys, L.P. v. Tolmar, Inc.*, 737 F.3d 731, 737-38 (Fed. Cir. 2013). Initiation times within this prior art range are presumptively obvious and

not overcome here by any unexpected results or evidence of criticality. *E.I. DuPont de Nemours & Co. v. Synvina C.V.*, 904 F.3d 996, 1006 (Fed. Cir. 2018) (“presumption of obviousness” for values within prior art range); § VIII.C, below.

Second, ESC Guidelines teaches initiating secondary preventative therapy at or prior to post-MI hospitalization discharge, corresponding to around day 2 or 3 post-MI.⁵ It recommends that long-term secondary prevention therapy, such as statins, “should be started as early as possible” in the hospital once the patients are stabilized for “early and sustained clinical benefits,” and that failing to do so risks “[l]ow treatment adherence... and is associated with worse outcomes.” EX1009, 24, 30, 33; EX1049, ¶159. Initiating secondary preventatives at or prior to post-MI hospital discharge was also common practice. EX1049, ¶157; EX1009, 33; *see supra* § II.C.

Motivation to initiate colchicine treatment at or prior to post-MI hospitalization discharge, i.e., at around 2-3 days post-MI, was reinforced by other

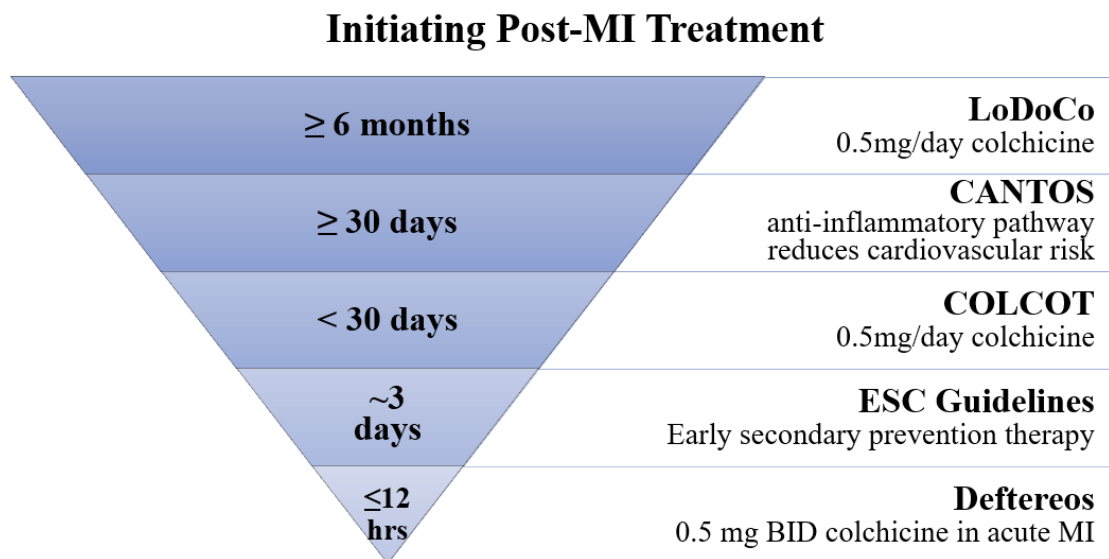
⁵ Consistent with a 2-3 day post-MI hospitalization period being common (EX1009, 24; EX1011, 1; EX1014, Abstract), ESC Guidelines note studies finding that “low-risk patients can safely be discharged from hospital on day 2 or day 3 after PCI,” i.e., around 2-3 days of the MI once the patient is stabilized. EX1009, 24, 13 (further teaching that the urgent care PCI is usually performed within 12 hours of an MI).

prior art reporting benefits associated with early post-MI initiation of secondary prevention treatments and recommending initiation before or at the time of hospital discharge. EX1049, ¶160; EX1008, 3, 6 (reporting that initiating post-MI statin therapy prior to or at hospitalization discharge⁶ showed a more pronounced reduction in 1-year mortality and concluding that “initiation of statin treatment before or at the time of hospital discharge should be recommended for AMI survivors” having cholesterol levels consistent with statin treatment because “the potential benefits seem substantial and adverse effects few....”); *see supra* § II.C.

As of 2019, multiple low-dose colchicine clinical studies designed to initiate treatment without delay in MI or stroke patients documented the expectation that “[c]olchicine could be a safe and effective inhibitor of the inflammation cascade induced by extracranial or intracranial atherosclerosis, providing thus an additional therapeutic agent in secondary noncardioembolic stroke prevention.” EX1044, 4; EX1040, 1; EX1046, 2, 3; EX1047, 6; EX1048, 4; EX1049, ¶¶49-53, 161-165. For example, Deftereos reported that initiating low dose colchicine within 12 hours post-

⁶ As Dr. Ridker explains, although Stenestrand is based on a study of Swedish patients in the 1990s with the mean hospitalization period had been 7.06 days, by 2019, the post-MI hospitalization period had been reduced to be typically less than about 3 days. EX1049, ¶160, n.210; EX1008, 3, 4; EX1011, 1.

MI was “safe use in patients with cardiovascular disease.” EX1040, 1; EX1044, 4; EX1049, ¶¶49, 162. As shown below, this momentum would have further motivated a POSA to initiate colchicine treatment at or prior to post-MI hospitalization discharge, i.e., at around 2-3 days post-MI. EX1049, ¶¶161-165.



In view of ESC Guidelines, the common knowledge and practice in the art, and multiple ongoing colchicine trials without any delay in treatment initiation, a POSA would have been motivated to initiate administration of colchicine—already shown effective in LoDoCo—prior to or at hospitalization discharge, i.e., at about 2-3 days of the MI, to “increase[] patient adherence” and to obtain “early and sustained clinical benefits.” EX1009, 33; EX1049, ¶¶158-165.

**iii. Reasonable Expectation of Success in
Reducing Risks of Cardiovascular Events
by Initiating Colchicine Treatment
Within About 3 Days Post-MI**

Those skilled in the art would have reasonably expected that initiating colchicine treatment early, including within about 3 days post-MI, would reduce (relative to an untreated patient) future cardiovascular events. EX1049, ¶¶166-172.

As discussed above, Nidorf had already successfully demonstrated reducing “the risk of a cardiovascular event, including an ACS, out of hospital cardiac arrest and non-cardio-embolic ischemic stroke” in cardiovascular disease patients (including those with past acute MI) that had been stable for at least 6 months by administering 0.5 mg daily colchicine, reporting that LoDoCo achieved “evident” benefit and substantially reduced cardiovascular risks. EX1007, 21:55-59, 20:34-36; EX1049, ¶¶28, 69, 167. Building on Nidorf’s demonstrated efficacy, a POSA would have expected that initiating colchicine treatment at about 3 days post-MI would also be effective to reduce the risk of future cardiovascular events. EX1049, ¶151. Indeed, a POSA would have expected that initiating treatment in stabilized post-MI patient at or before hospitalization discharge would potentially provide increased compliance and earlier prevention of secondary cardiovascular events. EX1009, 33; EX1008, 6; EX1049, ¶171; §VIII.A.1.a.ii, *supra*.

By 2019, with the “inflammation hypothesis” of cardiovascular disease proven by CANTOS in patients at least 30 days post-MI, a POSA would have understood that Nidorf’s efficacy similarly resulted from targeting the same underlying inflammatory pathways. EX1039, 19; EX1044, 3; EX1026, 4, Figure 1; EX1049, ¶¶168-169. Based on this and in view of COLCOT Protocol teaching colchicine initiation within 30 days post-MI and Deftereos teaching safely improving biomarkers by colchicine initiation with 12 hours post-MI, a POSA would have reasonably expected that colchicine treatment initiated at any time following the initiation of MI stabilization—whether at 6 months, at 30 days, within 30 days, or within 3 days—would reduce cardiovascular risks by treating the underlying coronary artery disease. EX1049, ¶171; EX1019, 3; EX1006, 1; EX1040, 1.

More specifically, CANTOS was widely recognized as providing significant clinical validation that targeting inflammation—as colchicine does—reduces cardiovascular risks. EX1033, 1; EX1032, 1; EX1034, 1; EX1035, 1; EX1015, 1; EX1026, 4, Figure 1; EX1047, 6; EX1049, ¶¶47, 169. In view of LoDoCo’s success with colchicine and CANTOS’s effectiveness by initiating treatment as early as 30 days post-MI, a POSA would have reasonably expected similar success from colchicine treatment initiated within COLCOT Protocol’s 30-day post-MI window, especially when better patient compliance would be expected from in-hospital initiation within 2-3 days post-MI. EX1009, 33; EX1006, 2; EX1049, ¶171.

The expectation of success is even higher for claims not entitled to an effective filing date earlier than the actual filing date, as Tardif 2019 and Bouabdallaoui had reported success of 0.5 mg/day colchicine initiated within 30 days and about 3 days post-MI, respectively. EX1022, 2; EX1005, 5; EX1049, ¶153.

b. Claim 27

First, as explained in Section V.B, the claim 27 preamble “reducing the risk of a stroke” is an intended purpose that does not require efficacy. Nevertheless, Nidorf teaches that LoDoCo

demonstrates that the addition of *colchicine 0.5 mg/day* to standard therapy in patients with stable coronary disease *significantly reduces the risk of* a cardiovascular event, including... *non-cardio-embolic ischemic stroke*.

EX1007, 21:55-59, 20:34-36; *see also id.*, 20:42-44 (“[o]ut of hospital cardiac arrest and *non-cardio-embolic ischemic stroke*⁷ were infrequent but were also *reduced in the treatment group*”); EX1049, ¶¶173-176. As explained above, Nidorf also teaches stratifying patients with past MI and, thus, teaches and renders obvious reducing stroke risk in patients who had an MI. COLCOT Protocol also teaches limitation 27[a], as further explained in Section VII.B.

⁷ Ischemic stroke is within the '063 patent “stroke” definition. EX1049, ¶176; EX1001, 6:23-27.

Second, limitation 27[b], which is substantively the same as limitations 1[b], 1[c], 8[b], and 8[c] and recites administering a daily low dose of colchicine, is taught by both Nidorf and COLCOT Protocol. *Supra* §§ VII.B and VIII.A.1.a.i.

Third, although Nidorf does not disclose limitation 27[c] (“within 30 days of the MI”), COLCOT Protocol teaches this limitation. EX1006, 5; EX1049, ¶171. As explained above, based on Nidorf’s demonstrated success in reducing stroke risk, multiple ongoing or completed colchicine trials treating patients with recent MI or stroke, and the known benefits of early secondary prevention treatments as reflected in ESC Guidelines, a POSA would have understood and been motivated to initiate colchicine treatment within 30 days of the MI with a reasonable expectation of reducing cardiovascular risk. *Supra* § VIII.A.1.a.

With respect to stroke more specifically, Nidorf 2013 confirmed that the rate of non-cardioembolic ischemic stroke reduced from 1.6% in the placebo group to 0.35% in the colchicine group.⁸ EX1020, Table 3; EX1049, ¶¶177-178. This

⁸ Although the reduced risk is based on a small number of events, it supports a reasonable expectation of success especially as it is directionally consistent with—and thus reinforces—what a POSA would expect from the statistically significant reduction of both LoDoCo’s composite primary outcome and the individual cardiovascular events within the composite. EX1007, 20:43-44 (reporting an

demonstrated effect provides a reasonable expectation of success for stroke risk reduction with shorter treatment initiation times of within 30 days post-MI. EX1049, ¶¶177-178. CANTOS's proof that targeting the inflammatory pathway as early as 30 days post-MI would reduce stroke risk reinforced the motivation and expectation of success. *Supra* § VIII.A.1.a.

Thus, the LoDoCo clinical data, in view of the mechanism of action as established by CANTOS, further support the motivation and expectation that 0.5 mg/day colchicine treatment, initiated within 30 days post-MI, would reduce the risk of a stroke. EX1049, ¶¶173-179.

Claim 27 would, therefore, have been obvious over Nidorf in view of COLCOT Protocol and ESC Guidelines.

2. Dependent claims

The dependent claims, which merely recite features either already taught by Nidorf and COLCOT Protocol or well known in the art, would also have been obvious over the Ground 3 references for the same reasons as discussed above for

average hazard ratio of 0.33 (0.18–0.59) and a P value of 0.001); EX1020, Table 3; EX1049, ¶¶177-178. Indeed, the same directional concordance of stroke reduction with a composite cardiovascular events outcome had also been observed in CANTOS. EX1019, Table 2; EX1049, ¶178.

the independent claims and as further discussed below. *Supra* § VIII.A.1. EX1049, ¶180.

a. Cardiovascular event claims 6-7, 9-11, and 50

As explained above, reducing the recited cardiovascular events—corresponding to elements in the LoDoCo and COLCOT Protocol primary outcomes—would have been obvious. *Supra* § VIII.A.1.a; EX1049, ¶¶181-183. Indeed, Nidorf specifically teaches reducing the risk of each cardiovascular event recited in claims 6-7, 9-11 and 50. EX1049, ¶¶64-69, 184.

For instance, Nidorf teaches:

analysis [of LoDoCo] confirmed that patients randomized to treatment were *less likely to present with an ACS* unrelated to stent disease (9/282 (3.2%) vs. 30/250 (12%) hazard ratio 0.26, 95% CI; 0.12-0.55; p<0.001), be it associated with an AMI [acute MI] ... or *UA* [unstable angina] (5/282 (1.8%) vs. 16/250 (6.4%) hazard ratio 0.27, 95% CI; 0.10-0.75; p=0.011).

EX1007, 20:50-55. Nidorf further teaches that “[o]ut of hospital *cardiac arrest* and *non-cardio-embolic ischemic stroke* were infrequent but *were also reduced in the treatment group*.” *Id.*, 20:42-44. Thus, Nidorf teaches reduction of the risks of each cardiovascular event individually recited in claims 6-7, 9-11, and 50. EX1049, ¶184.

In view of Nidorf’s success and ESC Guidelines, a POSA would have been motivated to reduce these same cardiovascular events in MI patients when the

treatment is initiated at a timing with potentially better patient compliance, e.g., within 2 or 3 days of the MI before hospital discharge. EX1049, ¶¶64-69, 181-184. Nidorf's success and CANTOS's consistent reduction of the recited cardiovascular events by targeting the same inflammatory pathways and initiating treatment earlier in time would have provided a reasonable expectation of success. EX1049, ¶¶168-169. Thus, for the same reasons discussed above for claims 1 and 8, these dependent claims would have been obvious. *Supra* § VIII.A.1.

In addition, Bouabdallaoui, which is prior art to these claims, reports reducing each recited cardiovascular events and concludes that “[e]arly initiation of low-dose colchicine after MI greatly reduced the risk of ischaemic CV events compared with placebo.” EX1005, 7, Table 3. Bouabdallaoui's reported efficacy would have reinforced the motivation to initiate colchicine treatment within about 3 days of the MI and the expectation of success in reducing each of the recited cardiovascular events. EX1049, ¶¶185-186.

b. Additional medication claims 2-5, 29-32, 40-43

Nidorf and COLCOT Protocol both teach these limitations. For instance, Nidorf discloses that the LoDoCo trial analysis was stratified by factors including “therapy with *aspirin*, clopidogrel or both, high dose *statin* therapy” and confirms that a high percentage of the enrolled patients were treated with aspirin and/or statin.

EX1007, 20:6-9, 21:25-54; EX1020, 13, Table 1; EX1049, ¶¶187-188. COLCOT Protocol similarly discloses these limitations. *See* § VII.B.2, above.

As Nidorf acknowledges, although aspirin and statins had been used as standard secondary prevention therapies for MI patients, “patients with atherosclerotic vascular disease continue to be at risk of cardiovascular events, possibly because these treatments fail to target some of the inflammatory pathways implicated in the disease.” EX1007, 2:35-38. EX1047, ¶25. Thus, consistent with the LoDoCo trial and COLCOT enrolling these patients, there would have been a motivation to initiate colchicine treatment to target the inflammatory pathways in patients who received aspirin or statin. *See* EX1047, ¶25.

Nidorf further provides a motivation and reasonable expectation of success for using colchicine for secondary prevention in patients that had been treated with aspirin or statins. For example, it teaches that the cardiovascular event composite primary outcome was “less in patients receiving colchicine and at least aspirin (4.67%) than in patients receiving at least aspirin but no colchicine (14.7%).” EX1007, 21:11-17. Thus, Nidorf’s success supports the motivation and expectation of reducing cardiovascular risks in MI patients that were prescribed with aspirin or statins by further administering daily low dose colchicine within about 3 days post-MI. EX1049, ¶¶189-192.

c. Patient population claims 12, 26, 33, 44, 48, and 49

As Dr. Ridker explains, the recitation in claims 12, 33, and 44 that “the patient has atherosclerotic coronary artery disease” merely identifies the obvious to treat underlying disease known to be common in MI patients. EX1049, ¶¶193-194; EX1015, 1; EX1006, 2. Nidorf is consistent, teaching and claiming a method of reducing the risk of a cardiovascular event “wherein the subject has the symptoms of or is diagnosed with atherosclerotic vascular disease.” EX1007, 2:35-36, 19:6-8, claims 1 and 22; EX1049, ¶195. Nidorf further teaches a need for “a long-term reduction in cardiovascular events in patients with clinically stable atherosclerotic vascular disease” and reported LoDoCo’s success in satisfying the need. EX1007, 2:45-48, Example 1. In view of these teachings and ESC Guidelines teaching better compliance within hospital stays, it would have been obvious to treat MI patients with underlying atherosclerotic vascular disease, as claimed, with a reasonable expectation of success. EX1049, ¶¶158-160, 193-197.

Treating “an adult human,” as recited in claims 26, 39, and 49, is also rendered obvious by Nidorf and COLCOT Protocol, as the former discloses treating patients “aged 35 to 85 years old” and the latter teaches treating “[m]ales and females of at least 18 years of age.” EX1007, 18:33; EX1006, 5; EX1049, ¶¶198-199.

d. “Initiation upon assessment” claims 13, 36, 46

First, the “administration of colchicine is initiated upon assessment in... (b) the hospital” limitation covers initiating colchicine treatment prior to patient discharge from the typically about 3-day post-MI hospitalization. *See* EX1049, ¶118. It thus would have been obvious for the same reasons as the “within about 3 days” limitation. EX1049, ¶¶200-201; *supra* § VIII.A.1.

Second, Nidorf and COLCOT Protocol teach that both LoDoCo and COLCOT were conducted at well-known hospital facilities, teaching this limitation. EX1007, 18:10-11; EX1006, 7; EX1049, ¶202. Indeed, assessing hospitalized patients was standard practice. EX1049, ¶¶203-204. ESC Guidelines further recommended initiating secondary prevention treatments during a hospital stay, which would necessarily require assessment of the patients in the hospital before treatment initiation. EX1009, 30, 33; EX1049, ¶¶84, 158-159. In view of these teachings and Nidorf’s success, a POSA would have been motivated to assess patients in a hospital setting, as claimed, with a reasonable expectation of success.

e. Dose and frequency claims 17-25, 34-35, and 45

These limitations are taught by Nidorf’s disclosure of administering 0.5 mg/daily colchicine and COLCOT Protocol’s disclosure of “0.5 mg tablet of colchicine taken once a day,” and thus would have been obvious for the same reasons as stated in Section VIII.A.1. EX1049, ¶205; *supra* §§ VII.A1 and VIII.A.1.

f. Tablet claims 14-16, 37-38, and 47-48

It would have been obvious to implement the method of claims 1, 8, and 27 with film-coated colchicine tablets, as recited in these claims. EX1049, ¶¶206.

As explained in Section VIII.A.1, independent claims 1, 8, and 27 would have been obvious over Nidorf in view of COLCOT Protocol, ESC Guidelines and COLCRYS teaching FDA-approved “film-coated, capsule-shaped [colchicine] tablets.” EX1016, 9; EX1049, ¶¶207-208. In view of the established suitability of film-coated colchicine tablets for oral administration, including improved appearance, taste, and ease of use by the patient, a POSA would have been motivated to administer colchicine as film-coated tablets, as claimed, with a reasonable expectation of success. EX1049, ¶¶208-209.

The obviousness of using film-coated colchicine tablets is reinforced by:

1. Patent Owner’s admission that “[v]arious colchicine formulations, including film-coated tablets, are readily available and well known in the art.” EX1001, 5:46-47; *Qualcomm Inc. v. Apple Inc.*, 24 F.4th 1367, 1375-76 (Fed. Cir. 2022) (“patentee’s admissions about the scope and content of the prior art provide a factual foundation as to what a skilled artisan would have known at the time of invention”);
2. Nidorf’s teaching that “[t]he active ingredient colchicine as well as its tablet formulation is listed in various national

and international pharmacopeias such as the United States Pharmacopeia (USP)” and that “[i]n all known indications, [colchicine] is generally administered orally as solid tablets in strengths of 0.5-0.6 mg/tablet (e.g. Europe and United States, respectively).” EX1007, 6:26-29, 6:40-43; EX1036, 4 (colchicine USP); EX1038, ¶¶33-35; EX1049, ¶207; and

3. COLCOT Protocol disclosing that colchicine is administered as “0.5 mg tablet,” meeting the tablet limitation. EX1006, 3.

g. “Within 4 to 7 Days” in claim 28

Dependent claim 28, which narrows the “within about 30 days of the MI” period of claim 27 to “within 4 to 7 days,” would also have been an obvious option within COLCOT Protocol’s 30-day post-MI administration window. *Infra*, § VIII.A.1.a.ii; EX1049, ¶¶210-216; *Galderma*, 737 F.3d at 737-38; *DuPont*, 904 F.3d at 1006.

There would have been a specific motivation and a reasonable expectation of success to initiate colchicine treatment post-MI during follow-up care, e.g., within days 4-7 post-MI, if the treatment had not already been started during hospitalization. EX1049, ¶¶211-216. For example, ESC Guidelines’ recommendation for “early post-discharge consultations” and the well-publicized “See you in 7” program focusing on this early post-discharge period for “long-term medication adherence”

would have further motivated a POSA to initiate colchicine treatment within 4-7 days post-MI (if not already initiated). EX1009, 24; EX1013, 1; EX1049, ¶¶213-214.

Accordingly, for post-MI patients who did not initiate secondary prevention treatment during the typical 3-day hospital stay period, a POSA would have been motivated to initiate the treatment during the closely monitored early post-discharge period. EX1049, ¶¶211-215. There would have been a reasonable expectation that initiating treatment within the early post-discharge period of 4-7 days would reduce stroke risk in view of Nidorf's and CANTOS's successes in stroke risk reduction, for all the same reasons as addressed above for claims 1, 8, and 27. EX1049, ¶216.

B. Ground 4: Claims 1-26, 28, and 40-50 Would Have Been Obvious over Bouabdallaoui in View of COLCRYS

For the same reasons discussed in Section VII.A, Bouabdallaoui anticipates as well as renders obvious claims 1-13, 17-26, 28, 40-46, 49, and 50.

Regarding claims 14-16, 47, and 48 that further recite colchicine in a tablet, coated tablet, or film-coated tablet form, as discussed above in Section VIII.A.2.f, it would have been routine and obvious to combine the teaching of COLCRYS with methods of administering colchicine (Bouabdallaoui) and administer film-coated colchicine to MI patients for the same reasons as in Ground 3. *See* § VII.A.2.f, *supra*.

Thus, claims 1-26, 28, and 40-50 would have been obvious over Bouabdallaoui in view of COLCRYS. EX1049, ¶¶217-219.

C. No Objective Indicia

The '063 patent's *post hoc* analysis of the COLCOT trial data in patients receiving colchicine “within about 3 days” of the MI, which Applicant characterized as unexpected results during prosecution, EX1002, 332-33, fails to establish nonobviousness at least because:

1. for claims not entitled to priority earlier than November 13, 2020, the same results were already published and therefore could not have been unexpected;
 2. the data fails to demonstrate unexpected superiority or criticality of within 3 days (claims 1-26 and 40-50) or within 4-7 days post-MI (claim 28) relative to COLCOT Protocol's 30-day window;
 3. the data do not show improved stroke reduction within 30 days of the MI (claims 27 and 29-39) compared to the LoDoCo trial; and
 4. the patent data are not commensurate with the claim scope.
- EX1049, ¶¶220-248.

1. The results had already been published in Bouabdallaoui

As explained above, Bouabdallaoui, which is prior art to claims 1-26, 28, and 40-50, already disclosed the patent's “within about 3 days” *post hoc* analysis. *Supra* §§ III.C and VIII.A. These known results cannot have been “unexpected.” *Wm. Wrigley Jr. Co. v. Cadbury Adams USA LLC*, 683 F.3d 1356, 1363 (Fed. Cir. 2012)

(patent owner “needed to demonstrate that the results were unexpected to a significant degree beyond what was already known”).

2. No criticality of “within about 3 days of the MI”

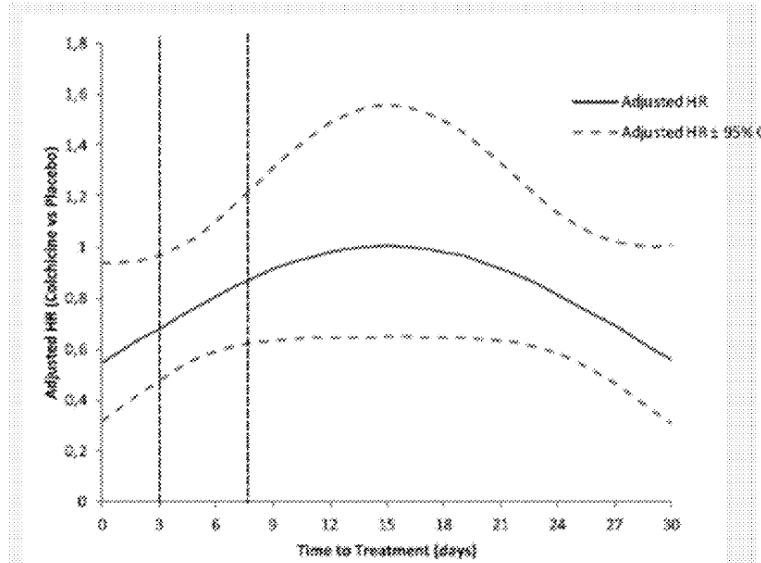
COLCOT Protocol specifically taught the dominating range of within 30 days post-MI, yet the patent data fail to show any criticality, much less “unexpected” benefit, of the “within about 3 days of the MI” limitation, compared to later initiation times within disclosed the 30-day range. Where, as here, there is “an absence of evidence indicating that there is something special or critical about the claimed range, an overlap suffices to show that the claimed range was disclosed in—and therefore obvious in light of—the prior art.” *Almirall, LLC v. Amneal Pharms. LLC*, 28 F.4th 265, 272 (Fed. Cir. 2022). Instead, the “within about 3 days” “cutoff point... appears to be arbitrary” where “nothing particularly unusual occurs....” *Milliken Research Corp. v. Dan River, Inc.*, 739 F.2d 587, 602 (Fed. Cir. 1984).

First, as Dr. Ridker explains, and as Dr. Fiolet and others independently observed, the data in the '063 patent (also published in Bouabdallaoui) fail to show any significance differences between the TTI groups of 0-3 days, 4-7 days, and 8-30 days. EX1001, Table 3; EX1049, ¶¶227-228, 234-241; EX1012, 4 (“The authors of [Bouabdallaoui] did not report whether the differences in observed effect size between strata were statistically significant.”); EX1038, ¶29. To the contrary, reflecting an absence of statistically significant differences and failure to establish

differences (beyond chance) between the groups, patent Table 3 shows that the primary composite endpoint hazard ratio range for 0-3 days overlaps with the ranges for 4-7 and 8-30 days TTI. EX1001, Table 3; EX1049, ¶230. Indeed, Bouabdallaoui itself admits that “these differences between groups did not reach statistical significance.” EX1005, 4.

Second, leaving aside the absence of statistical differences, as Dr. Ridker and Dr. Fiolet each explain, the parabolic shape of patent Figure 2 does not make biological sense and could result from “a play of chance” due to insufficient randomization among the *post hoc*-defined subgroups. EX1049, ¶¶243-245; EX1027, 9; EX1012, 3-4 (“[a]n important caveat in the interpretation of this finding is that not all unequally distributed characteristics were used in adjustment of these estimators”), 4 (“whether this parabolic relation of treatment initiation and effect size—with greater effect size seen in both very early (<3 days) and very late (>21 days) treatment initiation—reflects separate biologic mechanisms of the drug or is *a play of chance* cannot be distinguished from these data”); EX1001, Table 2 (showing reduced baseline hypertension, prior MI, and stroke or TIA in 0-3 day group).

FIG. 2



Third, patent Tables 3 and 10 (reproduced below with highlights) show that stroke risk reduction hazard ratio ranges substantially overlap for (1) 0-3 days (0.21), (2) 4-7 days (0.28 HR), (3) 8-30 days (0.19 HR), (4) LoDoCo (0.25 HR), and (5) COLCOT (0.23 HR). EX1001, Tables 3 and 10; EX1049, ¶¶229-230.

TABLE 3

Efficacy endpoints according to TTI (N = 4661, colchicine vs. placebo)			
Endpoints	TTI 0-3 days, N = 1193	TTI 4-7 days, N = 720	TTI ≥ 8 days, N = 2748
	Colchicine vs. placebo no. (%) HR (95% CI); p	Colchicine vs. placebo no. (%) HR (95% CI); p	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
Urgent hospitalization for angina requiring coronary revascularization	6 (1%) vs. 17 (2.9%) 0.35 (0.14-0.88); p = 0.026	4 (1.1%) vs. 6 (1.7%) 0.63 (0.18-2.24); p = 0.476	15 (1.1%) vs. 26 (1.9%) 0.61 (0.32-1.16); p = 0.131

TABLE 10

Study efficacy outcomes							
LoDoCo ¹¹		COLCOT ¹⁰		COPS ¹³		LoDoCo2 ¹²	
Colchicine N = 250	Control N = 282	Colchicine N = 2366	Placebo N = 2379	Colchicine N = 396	Placebo N = 399	Colchicine N = 2762	Placebo N = 2760
Primary composite outcome: Cardiovascular mortality, myocardial infarction, ischemic stroke, urgent revascularization							
Ischemic stroke							
Events, N (%)	1 (0.4%)	4 (0.2%)	16 (0.7%)	2 (0.5%)	6 (1.5%)	16 (0.6%)	24 (0.9%)
HR (95% CI)	0.23 (0.03-2.03)	0.25 (0.08-0.75)		0.34 (0.07-1.70)		0.66 (0.35-1.25)	

As such, the data does not show unexpected superiority or *any criticality* of initiating colchicine treatment “within about 3 days of the MI” as compared to other times within 8-30 days. EX1049, ¶229. Nor does it show unexpected superiority of initiating treatment “within about 3 days” or within 30 days relative to the prior art LoDoCo trial. EX1049, ¶230; EX1001, Examples 1 and 2; *Application of Merchant*, 575 F.2d 865, 869 (C.C.P.A. 1978) (“An applicant relying upon a comparative showing to rebut a prima facie case must compare his claimed invention with the closest prior art.”); *In re Geisler*, 116 F.3d 1465, 1469–70 (Fed. Cir. 1997).

Fourth, except claim 28, all claims encompass initiating treatment immediately, such as within 12 hours or 1 day, post-MI. EX1001, claims 1-50; EX1049, ¶232. However, the '063 patent does not include any data purporting to show efficacy, much less unexpected efficacy, for treatments initiated within this acute post-MI period. Nor would a POSA understand that results from the patent’s broader and undifferentiated “0-3 day” category would apply to this early post-MI period where other conditions dominate. EX1049, ¶232.

Fifth, as shown below in patent Table 3 (highlights added), the 0-3 day groups comprise single digit colchicine and placebo patients for resuscitated cardiac arrest and stroke. Given the small number of events, the 0-3 day group hazard ratios ranges are broad (e.g., resuscitated cardiac arrest: 0.03 to 3.20, stroke: 0.02 to 1.81) and p

values not statistically significant (e.g., resuscitated cardiac arrest: 0.340, stroke: 0.156). EX1001, Table 3; EX1049, ¶¶236-239.

TABLE 3

Efficacy endpoints according to TTI (N = 4661, colchicine vs. placebo)			
Endpoints	TTI 0-3 days, N = 1193	TTI 4-7 days, N = 720	TTI ≥ 8 days, N = 2748
	Colchicine vs. placebo no. (%) HR (95% CI); p	Colchicine vs. placebo no. (%) HR (95% CI); p	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

The data thus fail to establish any actual difference or provide unexpected results to support the nonobviousness of reducing risks of stroke or resuscitated cardiac arrest (claims 10, 50). EX1049, ¶¶236-239.

3. No alleged unexpected results support claims 27, 28

First, as explained above, the patent data do not show improved stroke reduction within 30 days of the MI (claims 27 and 29-39) compared to the COLCOT Protocol or LoDoCo.

Second, the patent data for administration within 3 days post-MI is outside the scope of, and therefore does not support the non-obviousness of, claim 28 that

requires initiating administration 4-7 days post-MI. *Ashland Oil, Inc. v. Delta Resins & Refractories, Inc.*, 776 F.2d 281, 306 (Fed. Cir. 1985) (“the secondary considerations [based on products not covered by the claims] would not have had any relevance”).

Third, the '063 patent itself admits that its *post hoc* TTI data for the primary end point “did not reach statistical significance” for either days 4-7 or day 8 and after. EX1001, 11:31-12:26. Applicant further admitted during prosecution that “administration of colchicine between days 4 to 7 and on or after day 8 do not” “yield[] a statistically significant reduction in the composite of primary endpoints in comparison to a placebo.” EX1002, 332. These admissions confirm that the patent’s 3-day data is not representative of other time points, much less the full scope of “within about 30 days of the MI,” as recited in independent claim 27, and “within 4 to 7 days of the MI,” according to claim 28. EX1049, ¶¶246-248; *In re Kao*, 639 F.3d at 1068 (“Evidence of secondary considerations must be reasonably commensurate with the scope of the claims.”).

IX. DISCRETIONAL DENIAL OF INSTITUTION IS NOT WARRANTED

The Examiner erred in (1) selecting Hennessy as the closest prior art when Bouabdallaoui and COLCOT Protocol both have anticipatory teachings, and (2) allowing the claims based on elements understood to be missing from references he

addressed that are expressly taught by Nidorf, COLCOT Protocol, and Bouabdallaoui. Nor did the Examiner consider (i) the combination of Nidorf, COLCOT Protocol, ESC Guidelines, and COLCRYS, (ii) the combination of Bouabdallaoui and COLCRYS, (iii) extensive new evidence motivating the claimed early post-MI treatment without a pre-loading dose, and (iv) new evidence contradicting Patent Owner's alleged unexpected results.

Accordingly, as explained further below, institution is warranted to redress these errors. *Advanced Bionics, LLC v. MED-EL Elektromedizinische Geräte GmbH*, IPR2019-01469, Paper 6 (PTAB Feb. 13, 2020); *Becton, Dickinson & Co. v. B. Braun Melsungen AG*, IPR2017-01586, Paper 8 (PTAB Dec. 15, 2017) (precedential) (identifying “BD” factors (a)-(f) relevant to § 325(d)).

A. Grounds 1 and 2 – Bouabdallaoui, COLCOT Protocol, and COLCRYS

1. Bouabdallaoui and COLCOT Protocol were not addressed on the record

While Bouabdallaoui (EX1005) was submitted via IDS but not addressed on the record, COLCOT Protocol (EX1006) was not even before the Office. EX1002, 76. Although Applicant stated in an IDS that a “September 16, 2015” version of the COCLOT protocol was submitted, Applicant actually submitted a non-prior art version retrieved from the Clinicaltrial.gov website on March 15, 2021, that differs from the 2015 version, and this non-prior art was never addressed on the record.

EX1002, 315-323, 326. Moreover, compared to the 2015 version, EX1006 contains additional relevant teachings, such as identifying the location of the COLCOT study as “Montreal Heart Institute,” a hospital facility. EX1031, 6; EX1038, ¶24. Discretionary denial under BD factors (a)-(c) and *Advanced Bionics* factor 1 is not warranted in view of their unaddressed, unapplied, and additional disclosures. *Amazon.com, Inc. v. M2M Sols. LLC*, IPR2019-01205, Paper 14 at 16 (PTAB Jan. 27, 2020) (“a reference that ‘was neither applied against the claims nor discussed by the Examiner’ does not weigh in favor of exercising the Board’s discretion under § 325(d) to deny a petition”); *see also ResMed Inc. v. New York University*, IPR2022-00992, Paper 15 at 18 (PTAB Dec. 8, 2022) (finding that an asserted prior art reference similar to a submitted reference but containing additional teachings was not previously presented to the Office and considered by the Examiner).

2. The Examiner erred in finding Hennessey to be the closest prior art

The Examiner erroneously understood the “closest prior art” to be Hennessey (EX1028), which described a different colchicine study, and relied on Hennessey as the sole primary reference. *See supra* § III.B. The Examiner failed to apply either Bouabdallaoui or COLCOT Protocol, both of which are anticipatory and closer. EX1002, 397-399; *Supra* § VII; EX1049, ¶¶109-139.

As noted, Bouabdallaoui is prior art to all challenged claims not entitled to an effective filing date earlier than November 13, 2020, i.e., at least claims 1-26, 28 and 40-50. *Supra* § III.C. It is also the closest prior art to and renders these claims anticipated and/or obvious as it describes the same *post hoc* analysis of *the same* COLCOT trial results, with *the same* target patient population, *the same* colchicine dosing regimen, and *the same* reduction of risks of *the same* cardiovascular events on which these claims rely. *See supra* § VII.A.

COLCOT Protocol, prior art to all claims, similarly describes *the same* COLCOT trial protocol, with *the same* target patient population, and *the same* colchicine dosing regimen. *See supra* § VII.B. COLCOT Protocol is the closest prior art for any claim to which Bouabdallaoui is not prior art.

This “basic error” favors institution under BD Factor (e) and *Advanced Bionics* factor 2. *See Application of Merch.*, 575 F.2d 865, 868 (C.C.P.A. 1978) (“The board’s basic error resides in its determination that Pring was the closest prior art.”). Patent Owner’s abandonment of its related EP application after it was found to lack novelty reinforces that the ’063 patent Examiner erred in not making an anticipation rejection. *Novartis Pharm. Corp. v. Shilpa Pharma, Inc.*, IPR2022-00886, Paper 13 at 28-29 (PTAB Oct. 26, 2022) (finding EPO’s rejection of Patent Owner’s similar arguments is “instructive” and concluding that “we agree with the EPO”).

3. Allowance was based on the Examiner's erroneous understanding that elements were missing from the prior art

The Examiner further erred in allowing the claims based on elements he understood to be missing from the relied-upon art but are specifically taught by Bouabdallaoui and COLCOT Protocol. *Eli Lilly and Company v. Teva Pharm. Int'l GmbH*, IPR2022-00796, Paper 9 at 11-13 (PTAB Oct. 14, 2022) (instituting where the ground references disclose “precisely the teaching that the Examiner found was missing” when allowing the claims); *see also Apple Inc. v. Telefonaktiebolaget LM Ericsson*, IPR2022-00457, Paper 7 at 8 (PTAB Sept. 21, 2022) (finding Examiner erroneously overlooked disclosures in relevant cited art because it “was not discussed in any Office Action or Response” or “was [] the basis for a rejection”).

First, the Examiner erroneously found that the amendment “wherein [PCI] was performed for treating the patient’s MI” “narrows the scope of the claim set such that it no longer reads on the cited art.” EX1002, 383, 396-97. However, the PCI limitation is specifically taught by Bouabdallaoui and COLCOT Protocol, not addressed or relied upon by the Examiner. EX1006, 1; EX1005, 3-4; *see also supra* §§ VII.A.1 and VIII.A.1.a.i.

Second, Bouabdallaoui and COLCOT Protocol both disclose—identically to the '063 patent—using 0.5 mg/daily colchicine without any pre-loading dose, with Bouabdallaoui further reporting achieving efficacy using this regimen. EX1006, 1;

EX1005, 3-4; *see supra* § VII. The Examiner, however, erroneously found that “[t]here is no motivation to delete the loading dose of [Deftereos].” EX1002, 397-98. This conclusion was error as it overlooked the anticipatory teachings of efficacious colchicine administration without a preloading dose in Bouabdallaoui and COLCOT Protocol that provide exactly the motivation the Examiner understood to be missing. To the extent the Examiner was only considering motivation *within* Deftereos, that was clear legal error. *Intel Corp. v. Qualcomm Inc.*, 2022 WL 880681, at *3 (Fed. Cir. Mar. 24, 2022) (“[T]here is no requirement that a motivation to combine must be separately expressed in each prior art reference.”).

As such, the Examiner’s material mistakes of ignoring critical teachings in Bouabdallaoui and COLCOT Protocol further favors institution under BD factor (a)-(e) and *Advanced Bionics* factors 1-2. *Microsoft Corp. v. Surfcaster, Inc.*, IPR2022-00590, Paper 9 at 15-16 (PTAB Oct. 7, 2022).

B. Ground 3 - Nidorf in View of COLCOT Protocol, ESC Guidelines, and COLCRYS

The BD and *Advanced Bionics* factors also favor institution based on Ground 3 at least because it “relies on one or more additional references that were not before the Examiner” such that “the first part of the *Advanced Bionics* framework is not satisfied.” *CommScope Inc. v. TQ Delta, LLC*, IPR2022-01012, Paper 9 at 10-11 (PTAB Nov. 28, 2022). Specifically, none of Nidorf, COLCOT Protocol, ESC

Guidelines, and COLCRYS were submitted to the Office or are cumulative with references “extensively evaluated during examination” or were “the basis for rejection.”⁹ *Supra* § II.D; *Microsoft*, IPR2022-00590, Paper 9 at 15. This favors institution under *BD* factors (a)-(d) and *Advanced Bionics* factors 1.

New supporting evidence was also not considered, further weighing in favor of institution. For example, the Examiner only considered motivation to remove the pre-loading dose from Deftereos, but never considered motivation to modify the Nidorf and COLCOT Protocol colchicine treatments, both of which used 0.5 mg/daily colchicine without a preloading dose, by shortening their treatment initiation periods. *Supra* §VIII.A.1. Nor did the Examiner consider motivation from (i) the uncited ESC Guidelines to initiate secondary preventive treatment during or right after hospital discharge, e.g., within 2-3 days or within 4 to 7 days of the MI, and (ii) numerous large-scale placebo-controlled colchicine clinical studies using low dose colchicine to treat patients with recent MI or stroke without initiation delay. *Supra* § VIII.A.1.

⁹ Although another Nidorf patent (EX1018) and the September 16, 2015 COLCOT Protocol were submitted in IDS, EX1002, 75, 326, neither was discussed in any Office Action or Response. EX1002, 293-99, 305, 345-55, 358.

Moreover, although the Examiner generally found that “administer[ing] the appropriate dosage (i.e. 0.5 mg) of colchicine by any appropriate means, such as tablet, a coated tablet or a film-coated tablet” would have been obvious, EX1002, 298, he did not consider COLCRYS, which expressly teaches film-coated low dose colchicine that had been commercially available decades before the ’063 patent’s filing date, or consider the new combination of Nidorf, COLCOT Protocol, ESC Guidelines, and COLCRYS showing the obviousness of dependent claims 14-16, 37-38, and 47-48 in Ground 3. *Supra* § VIII.A.2.f.

These facts support institution under *BD* factors (a)-(d) and *Advanced Bionics* factors 1-2. *CommScope*, IPR2022-01012, Paper 9 at 10-11; *Netflix, Inc. v. DivX, LLC*, IPR2020-00558, Paper 10 at 40 (PTAB Aug. 26, 2020) (granting institution and explaining “[b]ecause the combination... was not considered by the examiner, we find consideration of the references and arguments based thereon to be materially different than the examiner’s previous consideration...”).

In support of Ground 3, Dr. Ridker provided additional evidence not considered by the Examiner. This included the knowledge and routineness of initiating secondary prevention treatments before MI patients are released from the hospital or during 4 to 7 days post-MI. EX1049, ¶¶60-63, 80-84, 147-153, 157-165, 211-215. Dr. Ridker, the Principal Investigator of CANTOS, also addressed the impact of CANTOS on the expectation of successful colchicine treatment of MI

patients in view of the LoDoCo trial's earlier success. EX1049, ¶¶34-36, 40, 47-48, 152, 168-171. Dr. Ridker further described the trend in low dose colchicine clinical trials to target patients with recent MI or stroke, including CLEAR-SYNERGY (OASIS-9), COLCARDIO-ACS, and CONVINCe, all of which further support the routineness and obviousness of initiating early colchicine treatment. EX1049, ¶¶43-53, 161-164.

Such highly relevant information and testimonial evidence was never considered and is not cumulative of that considered by the Examiner, further supporting institution under *BD* factor (f) and *Advanced Bionics* factor 2. *E.g.*, *Celltrion, Inc. v. Genentech, Inc.*, IPR2017-01140, Paper 31 at 13-14 (PTAB Jan. 25, 2018) (institution when, “taking the expert declaration... into account, Petitioner’s testimonial evidence presents the prior art in a new light.”).

Moreover, in allowing the claims, the Examiner mistakenly overlooked material teachings in cited prior art, an error that further favors institution under *BD* factor (e) and *Advanced Bionics* factor 2. For instance, the Examiner did not raise any prior-art-based rejections over claims reciting PCI and/or reducing risks of resuscitated cardiac arrest, stroke, or urgent hospitalization for angina, finding that those limitations were missing from his erroneous chosen “closest prior art,” Hennessy. *Supra* § III.B. In addition, the Examiner further understood Deftereos to teach all claim 1 limitations except the without preloading dose limitation and

allowed the claims based on the finding that “[t]here is no motivation to delete the loading dose of [Deftereos]” EX1002, 397-98. These limitations, however, are all expressly taught by Nidorf and COLCOT Protocol. *Supra* § II.D.

Because the Examiner, having erroneously found Hennessy to be the closest prior art and overlooked material disclosures in the submitted art, “the Office erred in a manner material to the patentability of the challenged claims.” *Microsoft*, Paper 9 at 15-16; *Advanced Bionics*, Paper 6 at 8 n.9 (“An example of a material error may include misapprehending or overlooking specific teachings of the relevant prior art where those teachings impact patentability of the challenged claims.”).

Thus, factors (a)-(f) and *Advanced Bionics Factors* 1-2 all weigh against denial of institution of Ground 3.

C. Ground 4 - Bouabdallaoui and COLCRY5

As explained above in Section IX.A, the Examiner’s material mistakes of picking the wrong “closest prior art” and ignoring critical anticipatory teachings in Bouabdallaoui already favor institution. Moreover, the Examiner also did not consider COLCRY5 or the combination of Bouabdallaoui and COLCRY5 in allowing the claims. EX1002, 298. These facts further support institution of Ground 4 under BD factors (a)-(e) and *Advanced Bionics factors* 1-2. *Microsoft*, IPR2022-00590, Paper 9 at 15-16.

X. Grounds for Standing

Petitioner certifies the Patent is available for IPR and Petitioner is not barred or estopped from requesting IPR challenging the patent claims on the grounds identified herein.

XI. Mandatory Notices Under 37 C.F.R. § 42.8 Pursuant to 37 C.F.R. § 42.8 Petitioner states as follows:

A. Real Parties-in-Interest (37 C.F.R. § 42.8(b)(1))

Murray & Poole Enterprises Ltd., AGEPHA Pharma FZ LLC, AGEPHA Pharma USA, LLC, and UPTTON Limited are the real parties-in-interest.

B. Related Matters (37 C.F.R. § 42.8(b)(2))

Petitioner is not aware of any related matters that would affect or be affected by this proceeding.

C. Lead and Backup Counsel and Service Information (37 C.F.R. §§ 42.8(b)(3) and (b)(4))

Lead Counsel	Backup Counsel
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Please address all correspondence to counsel at the addresses above. Petitioner consents to electronic service by email at the above email addresses and to IPR2023-01064@finnegan.com.

XII. CERTIFICATION UNDER 37 C.F.R. § 42.24(d)

Pursuant to 37 C.F.R. § 42.24(a)(1)(i), the foregoing **PETITION FOR *INTER PARTES* REVIEW** contains 13,759 words, excluding parts of this Petition exempted under § 42.24(a), as measured by the word-processing system used to prepare this paper.

Respectfully submitted,

Dated: June 16, 2023

By: /Mark J. Feldstein/
Mark J. Feldstein, Reg. No. 46,693

CERTIFICATE OF SERVICE

Pursuant to 37 C.F.R. §§ 42.6(e) and 42.105(a), the undersigned certifies that on June 16, 2023, a copy of the foregoing **Petition for *Inter Partes* Review** and **the associated power of attorney** were served by FedEx Priority Overnight on the correspondence address of record indicated in the Patent Office's Patent Center website for U.S. Patent No. 11,400,063:

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By: /William Esper/
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