

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 11,400,063

PATENT OWNER'S RESPONSE

Table of Contents

I.	INTRODUCTION	1
II.	BACKGROUND	3
	A. Treating Cardiovascular Events and Stroke is Challenging and Unpredictable.....	4
III.	CLAIM CONSTRUCTION.....	6
	A. “reducing the risk of a stroke in a patient after having an MI”	6
	B. The “wherein” clauses are material claim limitations.....	10
IV.	GROUND 1: BOUABDALLAOUI IS NOT PRIOR ART AND THUS CANNOT ANTICIPATE	13
V.	GROUND 2: ANTICIPATION OF CLAIMS 27, 29-36 AND 39 BY COLCOT.....	19
	A. Petitioner Has Not Met Its Burden to Show that the COLCOT Is Prior Art.....	19
	B. COLCOT Does Not Explicitly Teach Every Limitation of Claim 27	22
	C. COLCOT Does Not Inherently Disclose the Stroke Reduction Limitation	23
	D. Dependent Claims 29 to 36 and 39 are not Anticipated	28
	1. Additional medication claims 29-32 are not anticipated by COLCOT.	28
	2. The patient population limitations of claims 33 and 39 are not anticipated by COLCOT.	29
	3. The dose and frequency limitations of claim 34 and 35 are not anticipated by COLCOT.	30
	4. Initiation of treatment limitation of claim 36 is not anticipated by COLCOT.	30

VI. GROUND 3 –CLAIMS 1 TO 50 ARE NOT OBVIOUS OVER NIDORF, COLCOT, ESC GUIDELINES AND/OR COLCRYS	30
A. Independent Claims 1, 8, and 27	32
1. Nidorf and COLCOT fail to disclose each limitation of claims 1 and 8, nor render such obvious in view of the prior art.	32
2. Petitioner fails to meet its burden to establish that claim 27 is obvious over the prior art.....	48
B. The Dependent Claims of the '063 Patent Are Not Obvious Under Ground 3.....	51
1. The CV event reduction claims would not have been obvious in view of the prior art.	51
2. The additional medication claims are not obvious over the asserted prior art.	53
3. Patient population claims are not obvious over the prior art references.....	53
4. Claims 13, 36, and 46 initiation requirements are not obvious	53
5. Claims 17-25, 34-35, and 45's dose and frequency limitations are not obvious	54
6. Claims 14-16, 37-38, and 47-48 are not obvious.....	54
7. It was not obvious of the prior art to initiate treatment within 4 to 7 days of MI.....	54
VII. GROUND 4: CLAIMS 1-26, 28, AND 40-50 ARE NOT OBVIOUS OVER BOUABDALLAOUI IN VIEW OF COLCRYS.....	55
VIII. OBJECTIVE INDICIA SUPPORT NONOBVIOUSNESS.....	55
A. The Treatment Regimen(s) Claimed by the '063 Patent Unexpectedly Reduces the Risk of CV Events.....	56

**B. The Teachings in the Prior Art Would Have Made a
POSA Skeptical.....58**

Table of Authorities

Cases

<i>Allergan Sales, LLC v. Sandoz, Inc.</i> , 935 F.3d 1370 (Fed. Cir. 2019)	11, 12, 13
<i>Bettcher Indus., Inc. v. Bunzl USA, Inc.</i> , 661 F.3d 629 (Fed. Cir. 2011)	23, 28
<i>Boehringer Ingelheim Vetmedica, Inc. v. Schering-Plough Corp.</i> , 320 F.3d 1339 (Fed. Cir. 2003).....	6, 7, 10
<i>Bristol-Myers Squibb Co. v. Ben Venue Labs., Inc.</i> , 246 F.3d 1368 (Fed. Cir. 2001).....	8, 9
<i>Catalina Mkg. Int’l Inc. v. Coolsavings.com, Inc.</i> , 289 F.3d 801 (Fed. Cir. 2002).....	8
<i>Corning Glass Works v. Sumitomo Elec. U.S.A., Inc.</i> , 868 F.2d 1241 (Fed. Cir. 1989).....	27
<i>Daubert v. Merrell Dow Pharm., Inc.</i> , 509 U.S. 579 (1993).....	16
<i>Dynamic Drinkware, LLC v. National Graphics, Inc.</i> , 800 F.3d 1375 (Fed. Cir. 2015).....	14
<i>E.I. DuPont de Nemours & Co. v. Synvina C.V.</i> , 904 F.3d 996 (Fed. Cir. 2018).....	42
<i>Eaton Corp. v Rockwell Int’l Corp.</i> , 323 F.3d 1332 (Fed. Cir. 2003).....	8
<i>Eli Lilly & Co. v. Teva Pharms. Int’l GmbH</i> , 8 F.4th 1331 (Fed. Cir. 2021)	34, 47
<i>Galderma Lab’ys, L.P. v. Tolmar, Inc.</i> , 737 F.3d 731 (Fed. Cir. 2013).....	42
<i>Glaxo Inc. v. Novopharm Ltd.</i> , 52 F.3d 1043 (Fed. Cir. 1995)	24, 28
<i>Griffin v. Bertina</i> , 285 F.3d 1029, 1033 (Fed. Cir. 2002).....	10
<i>Hansgirg v. Kemmer</i> , 102 F.2d 212, 214 (C.C.P.A. 1939)	28
<i>Honeywell Int’l Inc. v. Mexichem Amanco Holding S.A. DE C.V.</i> , 865 F.3d 1348 (Fed. Cir. 2017)	35

<i>Impax Labs. Inc. v. Lannett Holdings Inc.</i> , 893 F.3d 1372 (Fed. Cir. 2018) ...	34, 37
<i>IMS Tech., Inc. v. Haas Automation, Inc.</i> , 206 F.3d 1422 (Fed. Cir. 2000).....	10
<i>In re Kahn</i> , 441 F.3d 977 (Fed. Cir. 2006)	41
<i>In re Montgomery</i> , 677 F.3d 1375 (Fed. Cir. 2012)	24, 28
<i>In re Peterson</i> , 315 F.3d 1325 (Fed. Cir. 2003)	42
<i>In re Rijckaert</i> , 9 F.3d 1531 (Fed. Cir. 1993)	23
<i>In re Soni</i> , 54 F.3d 746 (Fed. Cir. 1995).....	56
<i>Insite Vision Inc. v. Sandoz, Inc.</i> , 783 F.3d 853 (Fed. Cir. 2015).....	33
<i>Invitrogen Corp. v. Biocrest Mfg., L.P.</i> , 327 F.3d 1364 (Fed. Cir. 2003)	8
<i>Kennametal, Inc. v. Ingersoll Cutting Tool Co.</i> , 780 F.3d 1376 (Fed. Cir. 2015).....	29
<i>Kinetic Concepts, Inc. v. Smith & Nephew, Inc.</i> , 688 F.3d 1342 (Fed. Cir. 2012).....	58
<i>Knauf Insulation, Inc. v. Rockwool Int’l A/S</i> , 788 Fed.Appx. 728 (Fed. Cir. 2019).....	23
<i>KSR Intern. Co. v. Teleflex Inc.</i> , 550 U.S. 398 (2007)	34, 41
<i>Metabolite Labs. Inc. v. Lab. Corp. of Am. Holdings</i> , 370 F.3d 1354 (Fed. Cir. 2004).....	24, 26, 27
<i>Monarch Knitting Mach. Corp. v. Sulzer Morat, GmbH</i> , 139 F.3d 877 (Fed. Cir. 1998).....	33
<i>Novartis Pharms. Corp. v. West-Ward Pharms. Int’l Ltd.</i> , 923 F.3d 1051 (Fed. Cir. 2019).....	35, 42, 54
<i>PAR Pharm., Inc. v. TWI Pharm., Inc.</i> , 773 F.3d 1186 (Fed. Cir. 2014)	23, 24
<i>Personal Web Techs., LLC v. Apple, Inc.</i> , 917 F.3d 1376 (Fed. Cir. 2019).....	23
<i>Pharmacyclics LLC v. Alvogen Pine Brook LLC</i> , 556 F.Supp.3d 377 (D. Del. 2021).....	34

<i>Pitney Bowes, Inc. v. Hewlett-Packard Co.</i> , 182 F.3d 1298 (Fed. Cir. 1999).....	6
<i>Procter & Gamble Co. v. TevaPharm. USA, Inc.</i> , 566 F.3d 989 (Fed. Cir. 2009).....	56
<i>Rowe v. Dror</i> , 112 F.3d 473 (Fed. Cir. 1997).....	10
<i>St. Jude Medical, LLC v. Snyders Heart Valve LLC</i> , 977 F.3d 1232 (Fed. Cir. 2020).....	34
<i>Süd-Chemie, Inc. v. Multisorb Techs., Inc.</i> , 554 F.3d 1001 (Fed. Cir. 2009)	56
<i>Syntex v. Apotex</i> , 407 F.3d 1371 (Fed. Cir. 2005)	13
<i>Trintec Indus., Inc. v. Top-U.S.A. Corp.</i> , 295 F.3d 1292 (Fed. Cir. 2002).....	22
<i>WBIP, LLC v. Kohler Co.</i> , 829 F.3d 1317 (Fed. Cir. 2016)	58

Statutes

35 U.S.C. § 102	19
35 U.S.C. § 102(a)	16
35 U.S.C. § 102(b)	32
35 U.S.C. § 102(b)(1).....	17
35 U.S.C. § 102(b)(1)(A)	19

Rules

37 C.F.R. 1.132 (Rule 132).....	17
FED. R. EVID. 702	16

I. INTRODUCTION

Dr. Tardif surprisingly discovered a novel and improved method of treating cardiovascular (“CV”) events and preventing recurrent CV events with low-dose colchicine initiated early after a myocardial infarction (“MI”). Dr. Tardif sought and obtained the bargained for temporary monopoly for disclosing his life-saving inventions in U.S. Patent No. 11,400,063 (“the ’063 patent”). However, now, Petitioner seeks to employ legally erroneous principles and conclusory arguments to invalidate Dr. Tardif’s duly issued ’063 patent. Petitioner alleges four grounds of invalidity, and each fails to support a finding of anticipation and/or obviousness.

Petitioner’s Grounds 1 and 4 assert anticipation and obviousness, respectively, relying on the non-prior art reference Bouabdallaoui, and thus Petitioner cannot prevail on these grounds. Petitioner alleges the ’063 patent should be entitled a priority date no earlier than November 13, 2020, however, Petitioner provides no factual basis for such a finding. Rather, the ’063 patent is entitled a priority date of November 15, 2019, the filing date of U.S. Provisional Application No. 62/935,865 (“the ’865 provisional application”). Because Bouabadallaoui was not published until ten months later, it cannot be prior art to the ’063 patent. Even if the Board were to determine that the ’063 patent is entitled a November 13, 2020 priority date, Bouabdallaoui is not prior art, because it is the work of the named inventor that was published less than one year before this latest possible priority date.

Petitioner's Grounds 2 and 3 allege anticipation and obviousness, respectively, over the COLCOT Protocol ("COLCOT"), as well as Nidorf, ESC Guidelines, and COLCRYS. However, Petitioner has not met its burden to show that COLCOT was publicly available before the priority date of the '063 patent. Moreover, Petitioner's expert, Dr. Ridker, testified that he does not recall reviewing COLCOT, and would not rely upon such a document, because it is "a very brief summary." EX2071 at 136:8-137:1. COLCOT is also missing key limitations that are critical to the patentability of the claims. Finally, Petitioner relies on hindsight bias in arguing that a person of ordinary skill in the art ("POSA") would have had a motivation to combine disparate prior art references to arrive at the claimed inventions with a reasonable expectation of success. But no such motivation or reasonable expectation existed.

Finally, Petitioner ignores the objective indicia that weigh heavily in favor of nonobviousness. A POSA would recognize the unexpected results from the treatment regimens claimed in the '063 patent. Additionally, a POSA as of the priority date would have been skeptical that the inventions of the '063 patent would work as claimed without a loading dose.

For the reasons explained herein, Petitioner has failed to meet its burdens to show invalidity of the '063 patent and Patent Owner respectfully request the Board

uphold the patentability of the life-saving treatment methods claimed in the '063 patent.

II. BACKGROUND

The inventions disclosed in the '063 patent are directed to the treatment and prevention of certain CV events in patients administered a regimen of low-dose colchicine shortly after a percutaneous coronary intervention. The use of colchicine in treating CV events has been considered since at least 1992, but its usefulness had not been substantiated. *See* EX2009. Further research taught that for many patient populations and treatment regimens, low-dose colchicine was ineffective regardless of the hypothesized usefulness of disrupting the inflammatory pathway. *See, e.g.*, EX2054; EX1028; EX2055; EX2056. Indeed, the prior art had not taught the treatment methods claimed in the '063 patent, and a POSA would not have found it obvious to arrive at the claimed inventions, particularly in view of the unpredictability in the field and failure of other similar studies.

Critically, colchicine operates very differently from other common anti-inflammatory agents, such as NSAIDS. EX2057 at 2-3, Table 1. Colchicine is known to disrupt the typical inflammatory response in CV events and lessen further damage by disrupting the common inflammatory pathway and plaque formation. *Id.*

A. Treating Cardiovascular Events and Stroke is Challenging and Unpredictable

The treatment, prevention, and recurrence of CV diseases is highly unpredictable. The unpredictability of the effectiveness of treatments is exacerbated when applied to certain patient populations, such as those who recently experienced an MI. EX2072 at ¶¶ 13-15. Many common, but severe, CV events were (and remain) well-understood to be attributable to multiple factors, and thus effectiveness of new therapies for preventing CV events is highly unpredictable. *Id.* For example, a POSA would have known that different studies investigated models for predicting recurrent CV disease with varying results. *See, e.g., compare* EX2073 *with* EX2074. A POSA would have also understood that even if the risk of recurrent CV events was known to increase, “[p]redictors and prognosis of a recurrent MI with contemporary management are not well known.” EX2058; *see also* EX2059 (teaching that risk window for post-MI stroke was longer than thought, but still not well-understood). While it was known that inflammation can play a role in the treatment of CV events and the prevention of recurrent events, and colchicine was understood to act as an anti-inflammatory before 2019, the scope of inflammation’s role and colchicine’s effectiveness to treat and prevent CV events was highly unpredictable.

Although some research suggested that reducing inflammation without affecting lipid levels can reduce the risk of CV disease, other research demonstrated

that there may be no causal or specific correlation between high-sensitivity C-reactive protein (“hs-CRP”) level and coronary heart disease. *See* EX2072 at ¶ 15; EX2060; EX2061; EX2062. The nine most relevant publications regarding studies of colchicine’s effectiveness in treating and preventing CV events demonstrate the high degree of unpredictability in targeting protein inhibition for inflammatory pathway disruption to treat or prevent CV events and disease. *See* EX2009; EX2054; EX2064; EX1020; EX2065; EX2055; EX1028; EX1022; and EX2056.

O’Keefe, Raju, Hennessy, Akodad, and Tong found that low-dose colchicine was ***not effective*** to treat certain CV events when compared to placebo. Conversely, Deftereos 2013, Nidorf 2013, Nidorf 2020, and Tardif 2019 showed that low-dose colchicine could be effective at treating certain CV events when compared to placebo. The failure of O’Keefe, Raju, Hennessy, Akodad, and Tong demonstrate the high unpredictability of the field, the lack of any reasonable expectation of success, and supports objective indicia of nonobviousness. Later studies including Shah failed to show reduction in PCI-related MI or major cardiovascular events (*see* EX2066 at 1) providing further evidence of the continued unpredictability in the field.

Moreover, a POSA would recognize that to determine which CV events and regimens low-dose colchicine is effective for would require extensive and expensive

clinical trials. EX2072 at ¶ 17. These reasons overwhelmingly demonstrate that the field of the invention was unpredictable.

III. CLAIM CONSTRUCTION

There are two similar but distinct claim construction disputes regarding the reduced risk of a subsequent cardiovascular event, including stroke, in patients who have suffered an MI. The first is whether the preambles of claims 27-39 that require “reducing the risk of a stroke in a patient after having an MI,” are limiting. The second is whether the wherein clause claiming a reduced risk of a cardiovascular event relative to a patient not being treated with colchicine, is a material claim element that limits the claim scope. The case law supports Patent Owner’s position that both the preamble and the wherein clauses at issue are material claim limitations that must be read into the claims as opposed to a mere “purpose” or “result.”

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

With respect to claims 27-39, a preamble is limiting when it is “‘necessary to give life, meaning and vitality’ to the claims” and describes the “essence of the invention.” *Boehringer Ingelheim Vetmedica, Inc. v. Schering-Plough Corp.*, 320 F.3d 1339, 1345 (Fed. Cir. 2003); *Pitney Bowes, Inc. v. Hewlett-Packard Co.*, 182 F.3d 1298, 1305 (Fed. Cir. 1999). That is the case here, as it often is for method claims. *Boehringer*, 320 F.3d at 1345 (preambles “frequently” embody the “essence of the invention” for method claims). Reducing the risk of cardiovascular events,

including stroke, in patients who have suffered a MI is the *raison d'être* of the claimed method itself, and in claims 27-39 that critical element is recited only in the preamble. The Federal Circuit has held that “preamble language will limit the claim if it recites not merely a context in which the invention may be used, but the essence of the invention without which performance of the recited steps is nothing but an academic exercise.” *Boehringer*, 320 F.3d at 1034. Divorced from the essence of reducing the risk of stroke, the claimed method is reduced to nothing more than daily administration of low dose colchicine to a patient within about 30 days of an MI. This would cover treatment for any purpose or condition, even one that has nothing to do with reducing risk of stroke or other cardiovascular event, the very heart of the invention. *Id.* Recall that colchicine was already approved and used for treating conditions like gout and FMF, and it certainly was not the inventor’s intention nor the Patent Examiner’s understanding that the claims would cover such previous use in an entirely different condition.

The specification confirms that the preamble is limiting by demonstrating that the reduction of risk of certain cardiovascular events, including the reduction of stroke, in patients who have suffered an MI is the “essence of the invention.” *Boehringer*, 320 F.3d at 1345. These issues are the focus of the specification and Examples 1 and 2, which assess the safety and efficacy of methods of treatment using a low dose of colchicine in reducing the risk of a cardiovascular event post

MI. Moreover, the assessment was not a simple process. It involved designing, overseeing, gathering and analyzing information from an international multicenter, randomized, double-blind trial with a total of 4,745 patients over the course of two years. EX2011 at ¶¶ 17-20.

The prosecution history also supports a limiting construction, as the Examiner explicitly stated that a reason for allowance was that the prior art did not teach, show or suggest or make obvious the reduction in the risk of stroke. EX1002 at 399; *Invitrogen Corp. v. Biocrest Mfg., L.P.*, 327 F.3d 1364, 1370 (Fed. Cir. 2003) quoting *Catalina Mkg. Int’l Inc. v. Coolsavings.com, Inc.*, 289 F.3d 801, 808-809 (Fed. Cir. 2002) (citing *Bristol-Myers Squibb Co. v. Ben Venue Labs., Inc.*, 246 F.3d 1368, 1375 (Fed. Cir. 2001) (“clear reliance on the preamble during prosecution to distinguish the claimed invention from the prior art transforms the preamble into a claim limitation because such reliance indicates use of the preamble to define, in part, the claimed invention.”)).

Finally, the preamble is limiting “[w]hen limitations in the body of the claim rely upon and derive antecedent basis from the preamble.” *Eaton Corp. v Rockwell Int’l Corp.*, 323 F.3d 1332, 1339 (Fed. Cir. 2003). Here, limitations in the bodies of the claims (*e.g.*, “the method comprising initiating...” and “at a daily low dose to the patient...”). Without the preamble, these elements would lack an antecedent basis. *See id.*

Petitioner contends the preamble is not limiting because it merely recites the purpose or result of the claim. However, the Federal Circuit has made clear that a purpose or result is limiting where the limitation is material to distinguishing the claim over the prior art, needed to breathe “life, meaning and vitality to the claims,” describes the “essence of the invention,” and provides antecedent basis to other claim limitations. The cases relied upon by Petitioner are distinguishable as described more fully below.

Petitioner relies on *BMS v. Ben Venue*, 246 F.3d at 1375, for the proposition that a preamble identifying a purpose is not limiting. In that case the court found that the preamble “for reducing hematologic activity” was not limiting, but stated explicitly “this is not a case in which a new use of a process should be considered to be a limitation because that new use distinguishes the process over the prior art. Here, the preamble of “reducing the risk of stroke in a patient after having an MI” distinguishes the method of claim 27 and its dependent claims over the prior art. Thus, it is materially different from the situation in *BMS* where the preamble was not relied upon to distinguish the claims from the prior art.

Relying on the same *BMS* case, Petitioner argues and the Board reasoned that the preamble should not limit claim 27 because the preamble of “reducing the risk of a stroke” does “not result in a manipulative difference in the steps of the claim.” However, that is not the relevant inquiry. To determine whether a preamble is

limiting, the Federal Circuit looks at whether the preamble gives “life and meaning *to* the manipulative steps,” *Griffin v. Bertina*, 285 F.3d 1029, 1033 (Fed. Cir. 2002) (emphasis added), not whether it results in a manipulative difference. That is the case here: the reduction of the risk of stroke gives life and meaning to the method steps and therefore the preamble should be limiting. The Petitioner is wrong that the body of the claim defines a “structurally complete invention.” As explained above, the Examiner correctly determined that the preamble is limiting because the claimed method without the preamble is meaningless. The cases cited by Petitioner are inapplicable and distinguishable. See *IMS Tech., Inc. v. Haas Automation, Inc.*, 206 F.3d 1422, 1434 (Fed. Cir. 2000); *Rowe v. Dror*, 112 F.3d 473, 478 (Fed. Cir. 1997). *IMS Tech* and *Rowe* involve apparatus claims in drastically different fields, not method of treatment claims to treat diseases in human patients where preambles frequently embody the essence of the invention. *Boehringer*, 320 F.3d at 1345. The fact that Petitioner needs to go to such disparate arts to support its proposed construction further demonstrates the weakness of its position.

B. The “wherein” clauses are material claim limitations

The “wherein” limitations in claims 8-11 and 20-23—“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”—

are material limitations and not a mere result. Dependent claims 6 and 7 have similar wherein claim limitations of a lower risk of a cardiovascular event or ischemic cardiovascular event compared to a patient not being administered colchicine that must be construed as limiting, otherwise those dependent claims are also meaningless.

Petitioner also relies on the inapplicable *BMS* decision to argue that the two wherein clauses in claim 8 are non-limiting and do not add patentable weight to the claims because “it doesn’t result in manipulative difference in the step of the claim.” The relevant case law stands for the exact opposite result where, as here, the wherein clauses were relied upon for patentability. The *Allergan* decision is the most analogous to this case. *Allergan Sales, LLC v. Sandoz, Inc.*, 935 F.3d 1370 (Fed. Cir. 2019). There, the claims at issue were directed to “[a] method of treating a patient with glaucoma or hypertension.” Like the ’063 patent, the claims in *Allergan* had similar wherein clauses comparing results of the claimed method relative to a prior art method, stating:

“wherein the method is as effective as the administration of 0.2% w/v brimonidine tartrate monotherapy three times per day and *wherein* the method reduces the incidence of one o[r] more adverse events selected from the group consisting of conjunctival hyperemia, oral dryness, eye pruritus, allergic conjunctivitis, foreign body sensation, conjunctival folliculosis, and somnolence when compared to the administration of 0.2% w/v brimonidine tartrate monotherapy three times daily.” (emphasis added)

In construing the claim, the Federal Circuit affirmed the District Court’s ruling that the wherein clauses were limiting and rejected Sandoz’s arguments that the wherein clauses “merely state the intended results” of the method or that the results are not “material to patentability.” *Allergan*, 935 F.3d at 1374. Like the Petitioner here, Sandoz cited *BMS* and argued that the clauses merely stated intended results that were witnessed in the clinical trial discussed in the patent-in-suit. *Id.* The *Allergan* Court was not persuaded and unequivocally held that *BMS* and other similar cases were distinguishable because the clauses at issue were not material to patentability. *Id.* (“In [*BMS*] we expressly noted that the disputed claim terms ‘w[ere] voluntarily made after the examiner had already indicated...the claims were allowable’ and such ‘unsolicited assertions of patentability’ made during prosecution do not create a material limitation”). Here, however, as in *Allergan*, both MHI and the Examiner explicitly relied on the “wherein” clauses to distinguish the claimed methods over the prior art during prosecution. Thus, the ‘wherein’ clauses are not unnecessary or irrelevant, but material to the Examiner’s patentability determination, and the *Allergan* decision controls the analysis here.

Like Sandoz in *Allergan*, Petitioner also cites to the *Minton* case where the term “trading efficiently” was found to be a non-limiting intended result. The *Allergan* case also explained that “[i]n *Minton*, we reasoned that the term “efficiently” on its face does not inform the mechanics of how the trade is executed,

and nothing in the specification or the prosecution history suggests otherwise.” *Allergan*, 935 F.3d at 1379 (J. Prost, concurring). The Federal Circuit declined to apply *Minton* finding that the wherein clauses of reduced incidence of certain adverse events and relative efficacy are “clear and measurable metrics” and are not a vague intended result like “trading efficiently.” *Id.* Like the wherein limitations in *Allergan*, Claim 8 and its dependent claims in the ’063 patent have very similar clauses: “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.”

Lastly, Petitioner cites to *Syntex v. Apotex*, 407 F.3d 1371, 1378, to strike the wherein clauses, but *Syntex* is also distinguishable because the result of using a “stabilizing amount” was not material to patentability. Thus, the Board should find that the wherein clauses in claim 8 and its dependent claims are limiting.

IV. GROUND 1: BOUABDALLAOUI IS NOT PRIOR ART AND THUS CANNOT ANTICIPATE

Bouabdallaoui cannot anticipate the claims because it is not prior art. The ’063 patent, and all its claims, are entitled to a priority date of November 15, 2019, which is nearly ten months before the publication of Bouabdallaoui. *Compare* ’063 at Cover *with* Petition at 15. Petitioner crafts Bouabdallaoui into prior art by: (1) improperly assessing the ’063 patent’s priority date and (2) discrediting Dr. Tardif

of his own work to find “work of another.” Petitioner’s use of Bouabdallaoui as prior art should fail for either reason.

Petitioner bears the burden of proving unpatentability “and that burden never shifts to the patentee.” *Dynamic Drinkware, LLC v. National Graphics, Inc.*, 800 F.3d 1375, 1378 (Fed. Cir. 2015). Here, as in *Dynamic*, Petitioner bears both the burden of persuasion with regards to unpatentability and the burden of production that Bouabdallaoui anticipates the ’063 patent. Patent Owner’s Preliminary Response rebutted, with evidence from the inventor, Petitioner’s unsupported allegations that Bouabdallaoui is prior art, and that burden of production shifted back to Petitioner. However, as in *Dynamic*, Petitioner has yet to shift the burden of production back to Patent Owner with regards to key aspects of the prior art dispute. Thus, because Petitioner bears the burden of persuasion of unpatentability, and the burden of production regarding the applicability of Bouabdallaoui as prior art has been met by Patent Owner, Petitioner’s burden remains, and cannot be met for that reason alone. However, despite the burden of production remaining on Petitioner, Patent Owner now produces more evidence in the form of a declaration from Dr. Bouabdallaoui herself demonstrating the Bouabdallaoui reference is not prior art. *See* EX2068.

Petitioner incorrectly alleges that the limitations “within about 3 days of the MI” and “within about 4 to 7 days of the MI” is not disclosed in the ’865 provisional

application, and thus claims 1-26, 28, and 40-50 have a priority of November 13, 2020. Paper 1 at 19-20. Petitioner further alleges that the '865 provisional application describes the COLCOT trial protocol and emphasizes that “[p]atients were enrolled a mean of 13.5 days after myocardial infarction.” *Id.* However, Petitioner omitted that the '865 provisional application’s specification recited that “[i]n some embodiments, the method involves administering colchicine within 5, 10, 15, 20, or 25 days of the MI.” EX1004 at 2:32-34. Petitioner also omitted the fact that the *as-filed claims* of the '865 provisional application recited “administering colchicine within 5, 10, 15, 20, or 25 days of the MI.” EX2067 at Claim 2.

As an initial matter, the “within 4 to 7 days of the MI” recited in claim 28 is clearly disclosed by the '865 provisional application and recited in its claims. But, critically, the “within about 3 days of the MI” is also covered by the '865 provisional application’s specification and claim 2. “Within about 3 days of the MI” would include days 0, 1, 2, and 3 of the MI, which is also encompassed by the range of “within 5... days of the MI” from the '865 provisional application.

Moreover, Dr. Ridker testified at deposition that a POSA would understand that “within about 3 days of the MI” is encompassed by “within 5... days of the MI,” and Dr. Ridker opined that it is only the lower limit of stabilization that is critical to a POSA. EX2071 at 92:1-20. Moreover, Dr. Ridker was unable to articulate the rationale underlying his opinions in his declaration regarding the '063 patent’s

priority date. *Id.* at 86:16-92:20. Seemingly, Dr. Ridker applied the incorrect legal standard, and his opinions regarding the disclosures of the '865 provisional application are nothing more than attorney argument. When an expert does no more than espouse attorney argument or relies on erroneous legal standards to form an opinion, that opinion becomes unreliable for the trier of fact. *Daubert v. Merrell Dow Pharm., Inc.*, 509 U.S. 579, 597 (1993); FED. R. EVID. 702. Accordingly, here, the Board should disregard Dr. Ridker's opinions regarding the priority date of the '063 patent, particularly with regard to the limitations "within about 3 days of MI" and "within 4 to 7 days of MI."

Finally, Bouabdallaoui itself discloses the pending application for "methods for using low-dose colchicine after MI... assigned to the Montreal Heart Institute." EX1005 at 7. That application is the same '865 provisional application that was also disclosed in the Tardif 2019 reference, which necessarily predates both publications. EX1022 at 9.

Accordingly, the '063 patent is properly afforded the priority claimed from the '865 provisional application of November 15, 2019. Therefore, under 35 U.S.C. § 102(a), Bouabdallaoui was not published or publicly available "before the effective filing date of the claimed invention" and cannot anticipate the '063 patent.

Even if the Board finds that the '063 patent is not entitled to a priority date of November 15, 2019, Bouabdallaoui is still not prior art. Pursuant to 35 U.S.C. §

102(b)(1), “[a] disclosure made 1 year or less before the effective filing date of a claimed invention shall not be prior art to the claimed invention... if the disclosure was made by the inventor... or by another who obtained the subject matter disclosed directly or indirectly from the inventor.”

As Patent Owner explained in its Preliminary Response, Dr. Tardif, the sole inventor of the '063 patent, is also the lead author of Bouabdallaoui. Paper 6 at 4-8. As the lead author, Dr. Tardif declared that the Bouabdallaoui reference is a description of the results of the COLCOT clinical trial, which he designed, executed, and managed. EX2011. Dr. Tardif further explained that the article was his work, and the co-authors were attributed credit for their efforts in obtaining data and providing review of the transcript. *Id.* Therefore, Bouabdallaoui is a reference disclosing the inventor’s own work and cannot be considered prior art.

The Board recognized that there is no requirement for declarations from all of the authors of the article under Rule 132; Dr. Tardif’s declaration satisfies all the requirements for an inventor declaration. However, to put the issue to rest, Patent Owner has also obtained a declaration from Dr. Boubdallaoui herself. Dr. Boubdallaoui’s declaration confirms the key aspects of Dr. Tardif’s declaration, including that she was not involved in the COLCOT study underlying the article, that Dr. Tardif conceived of the study and is the lead author on the article, and that she does not consider herself an inventor of the '063 patent. EX2068.

But even before Dr. Bouabdallaoui's declaration was obtained, the evidence supported only one conclusion, that Dr. Tardif is the sole inventor. Petitioner does not provide any evidence to the contrary. First, it is undisputed Dr. Tardif is the corresponding author. Dr. Ardehali also corroborates this fact. EX2001 at ¶¶ 30-31. Dr. Tardif has submitted a sworn declaration that he is the sole inventor of the '063 patent, that the disclosures of the Bouabdallaoui reference are his or under his direction as the corresponding author. Dr. Tardif is the second listed author on the article and stated that he allowed Dr. Bouabdallaoui to be the first named author since she was early in her career and it would be helpful to have articles where she was listed first. However, there is no doubt that as corresponding author Dr. Tardif was the individual responsible for the article, spoke on behalf of the other authors and was responsible for edits, agreements and publishing the article. EX2011.¹

Petitioner has not shown Bouabdallaoui is prior art. There is no evidence that the subject matter of Bouabdallaoui is the inventive work of anyone but Dr. Tardif. Accordingly, and in view of Dr. Tardif's declaration, Bouabdallaoui would, *at best*,

¹ Petitioner also argues that Tardif 2019 is prior art supporting its invalidity grounds, but there is no allegation that Tardif 2019 is the work of another. Tardif 2019 discusses the COLCOT trial and reports on its results. EX1022. Although, Tardif 2019 does not include Dr. Bouabdallaoui as an author, because she was not involved in conducting the COLCOT study. And importantly, Tardif 2019 discloses the '865 provisional application, which further evidences that Dr. Bouabdallaoui is not an inventor of the '063 patent, nor the properly identified lead author of the Bouabdallaoui reference. See EX1022 at 9.

be a “disclosure... made... by another who obtained the subject matter disclosed directly or indirectly from [Dr. Tardif].” 35 U.S.C. § 102(b)(1)(A).

V. GROUND 2: ANTICIPATION OF CLAIMS 27, 29-36 AND 39 BY COLCOT

COLCOT does not anticipate claims 27, 29-36 and 39 because it does not disclose each and every limitation recited in those claims. For the reasons discussed above, the preamble of claim 27—which claims 29-32 and 39 depend—is limiting because it breathes life and meaning into the claimed method. Specifically, COLCOT does not disclose a risk reduction of stroke in the patient treated according to claim 27.

A. Petitioner Has Not Met Its Burden to Show that COLCOT Is Prior Art

Petitioner alleges that COLCOT is a prior art reference that anticipates claims 27, 29-36, and 39 of the '063 patent. It is universally understood in patent law that a reference can only anticipate patent claims if that reference was publicly available before the patent claims' effective filing date. 35 U.S.C. § 102. But Petitioner's evidence to establish COLCOT is prior art is unreliable at best, and Petitioner's own expert testified he would not rely on COLCOT. Therefore, Petitioner has failed to meet its burden of production to show that COLCOT protocol is prior art and is thus capable of anticipating claims 27, 29-36, and 39 of the '063 patent.

Petitioner relies on a document that purports to be an archive version of the FDA's clinical trials website. In support of the alleged authenticity of this document, Petitioner relies on the opinion of Mr. Cruitt. However, Mr. Cruitt is an employee of Finnegan, Henderson, Farabow, Garrett & Dunner, LLP, which is the same law firm that initially represented Petitioner. *See* Paper 2; EX1038 at ¶ 2. Mr. Cruitt is not an objective expert witness, and his biased opinion should be stricken and afforded no weight.

Not only is Mr. Cruitt's declaration not reliable due to bias as a result of fiduciary duty owed to his employer—Petitioner's law firm—but the FDA clinical trials website record history data does not comport with Mr. Cruitt's opinions. The record history reports the same or similar data regarding the timing of certain submissions and filings, however the public availability of the COLCOT protocol is listed as July 16, 2020. EX2069 at 13. Further calling into question Mr. Cruitt's analysis is the linked version of the study protocol, which is internally dated November 15, 2018, more than eighteen months *after* Mr. Cruitt alleges the protocol was publicly available. Critically, unlike Mr. Cruitt, the FDA's record history is an unbiased source of information regarding the submissions and publications on the FDA website for the COLCOT trial.

More critically, Petitioner's expert, Dr. Ridker himself undermined Petitioner's ability to rely on COLCOT to show invalidity under Ground 2.

At deposition Dr. Ridker testified under oath that he did not recall ever seeing COLCOT. EX2071 at 139:3-140:5, 140:8-141:15. In support of that testimony, Dr. Ridker further testified that he would not look to a [clintrials.gov](https://clinicaltrials.gov) summary reference to understand a trial's protocol, and instead would rely on the entire protocol as submitted to the FDA or a publication. *Id.* at 139:19-140:1, 146:11-147:11. Dr. Ridker was also shown the full protocol at deposition, which was listed as being publicly posted on July 16, 2020. *Id.* at 151:9-152:22; *see also* EX2069. Tellingly, Dr. Ridker testified that the full protocol is what he would rely upon to understand a trial. *See, e.g.*, EX2071 at 146:11-147:11.

Thus, like the priority date issue, here again, Dr. Ridker's declaration is nothing more than mere attorney argument. However, even worse here, the expert testified that he cannot recall reviewing—nor would Dr. Ridker rely on such a reference—an allegedly invalidating reference for anticipation. *Id.* at 139:3-140:5, 140:8-141:15. The Board should, at minimum, disregard Dr. Ridker's testimony regarding Ground 2, because that testimony is a repetition of attorney argument and the witness's admissions that he did not and would not rely on the reference make any testimony highly unreliable.

Accordingly, the evidence creates a material question regarding the authenticity of EX1006, particularly its status as "prior art." Tellingly, Petitioner and their expert do not provide any explanation for why the record history on the

FDA’s own website should be disregarded or is incorrect. Therefore, Petitioner has not met its burden of production to show that COLCOT disclosed as EX1006 is prior art sufficient to anticipate claims 27, 29-36, and 39 of the ’063 patent.

B. COLCOT Does Not Explicitly Teach Every Limitation of Claim 27

COLCOT is the FDA-required clinical trial design overview for the COLCOT trial designed by Dr. Tardif. As with any clinical trial protocol, the reference does not disclose the findings or results of the COLCOT study. Tellingly, it was the unexpected and surprising results from COLCOT that formed the basis of Dr. Tardif’s invention.

As with any clinical trial, COLCOT merely tested a “*hypothesis* that treatment of the underlying inflammatory process will contribute to improved cardiovascular clinical outcomes.” EX1006 at 4 (emphasis added). COLCOT discloses that colchicine is a potent anti-inflammatory drug approved for acute use in patients with gout and chronic use in patients with FMF. *Id.* But, there is no disclosure of a reduction in the risk of stroke. This alone negates the possibility of anticipation, which requires strict identity between the allegedly invalidating disclosure and the challenged claims. *Trintec Indus., Inc. v. Top-U.S.A. Corp.*, 295 F.3d 1292, 1296 (Fed. Cir. 2002). At most, COLCOT discloses there was some work that highlighted the “potential” of colchicine in the treatment of CV diseases mediated by pro-

inflammatory effects. A hypothesis, however, is woefully insufficient to meet the anticipation standard.

C. COLCOT Does Not Inherently Disclose the Stroke Reduction Limitation

Petitioner also alleges that COLCOT inherently anticipates claim 27. The burden to show inherency is on the Petitioner. *Knauf Insulation, Inc. v. Rockwool Int’l A/S*, 788 Fed.Appx. 728, 734 (Fed. Cir. 2019). Inherency cannot be established by mere possibilities or even probabilities. *Bettcher Indus., Inc. v. Bunzl USA, Inc.*, 661 F.3d 629, 639 (Fed. Cir. 2011). The fact that a certain result or characteristic may occur or may be present in cited art is not sufficient to establish the inherency of that result or characteristic. *In re Rijckaert*, 9 F.3d 1531, 1534 (Fed. Cir. 1993) (reversing rejection based on inherency because result due to optimization of conditions was not necessarily present in the prior art). Inherency of a claim limitation requires the inherent result to inevitably occur from the disclosed steps, and the result must occur every time. *PAR Pharm., Inc. v. TWI Pharm., Inc.*, 773 F.3d 1186, 1195 (Fed. Cir. 2014) (“The mere fact that a certain thing may result from a given set of circumstances is not sufficient.”); *Bettcher*, 661 F.3d at 639. Moreover, the Federal Circuit has held that “a party must ‘show that *the natural result flowing* from the operation as taught would result in the performance of the questioned function.’” *Personal Web Techs., LLC v. Apple, Inc.*, 917 F.3d 1376, 1382 (Fed. Cir. 2019) (emphasis in original) (quoting *PAR Pharm.*, 773 F.3d at

1195). COLCOT does not meet this strict standard for inherent anticipation. COLCOT merely provides an invitation to perform the clinical study. *In re Montgomery*, 677 F.3d 1375, 1380 (Fed. Cir. 2012) citing *Metabolite Labs. Inc. v. Lab. Corp. of Am. Holdings*, 370 F.3d 1354, 1367 (Fed. Cir. 2004) (“[a]n invitation to investigate is not an inherent disclosure”).

Here, although the post-hoc analysis conducted from the COLCOT study data showed a statistically significant reduction in the risk of stroke in a critical cohort of trial patients, such a reduction was not the natural and necessary result. EX1001 at 2:4-22. Indeed, both the '063 patent and the Bouabdallaoui reference (which discloses the same results recited in the patent specification) plainly show that some patients did not in fact experience a reduction in the risk of stroke, and thus the limitation is not inherent. *See Glaxo Inc. v. Novopharm Ltd.*, 52 F.3d 1043, 1047 (Fed. Cir. 1995) (finding no inherency where claim recited specific polymorph and prior art reference resulted in significant minority yield of unclaimed polymorph).

Petitioner's attempt to analogize this case to the *In re Montgomery* case fails. In that case, the Federal Circuit extended inherent anticipation to a method of treatment based on a reference disclosing a plan for a clinical trial using ramipril “for the treatment or prevention of stroke or its recurrence.” The *Montgomery* case is distinguishable for several reasons. Critically, in *Montgomery*, the patent owner did not provide evidence to rebut examiner's allegation of inherency. But here,

Patent Owner does offer such rebuttal evidence, including a study contemporary to COLCOT that showed treatment of low-dose colchicine does not reduce the risk of recurrent CV events, including stroke, in patients post-PCI.

Tong reports the results of the Australian COPS trial (“COPS”). Tong was published online ahead of print on August 29, 2020, the same day as Bouabdallaoui. *Compare* EX2070 with EX1005. Indeed, both studies were also presented at the European Society for Cardiology Congress from August 29 to September 1, 2020. EX1049 at ¶ 70. COPS investigated whether patients with acute coronary syndromes (“ACS”) could be effectively treated with colchicine in addition to standard secondary therapies. EX2056 at 1891. Like the patients in COLCOT, the patients in COPS included adults with ACS, including an MI, who underwent a PCI and were assigned to either a colchicine arm or a placebo arm. EX2056; EX1005. Moreover, the patients in the colchicine arm were initiated with 0.5 mg twice daily (with no loading dose) before hospital discharge. EX2056 at 1891-92. Patients remained on colchicine for twelve months with a dose reduction after one month of treatment. *Id.* The primary outcome in COPS was a composite of death from any cause, ACS, ischemia-driven urgent revascularization, and noncardioembolic ischemic stroke. *Id.* at 1892. However, unlike the results of COLCOT, COPS “demonstrated that in patients presenting with an ACS, the addition of low-dose oral colchicine to standard medical therapy during hospitalization and continued for 12

months did not affect the rate of the primary composite outcome of death, ACS, ischemia-driven urgent revascularization, and stroke compared with standard medical therapy alone.” *Id.* at 1895.

Thus, unlike the facts in *Montgomery*, here it cannot be said that the natural and necessary result of “initiating the administration of colchicine at a daily low dose to the patient within about 30 days of an MI” is a reduction in the risk of stroke. Compare EX1001 claim 27 with EX2056 at 1895. Indeed, the reduction of risk for stroke in patients according to claim 27 was surprisingly discovered by Dr. Tardif and first recited in the ’856 provisional application’s claim 10.

Moreover, like previous findings from the Federal Circuit, COLCOT simply invites a POSA to investigate, and is not an inherent disclosure of the claimed invention. *Metabolite Labs.*, 370 F.3d at 1367 (“An invitation to investigate is not an inherent disclosure.”). In *Metabolite Labs.*, the Federal Circuit found that a reference that did not disclose the correlation of homocysteine and cobalamin folate deficiencies, could not anticipate a patent that required those correlations because the prior art simply invites further experimentation, which is the case here. COLCOT does not disclose the correlation between low-dose colchicine in post-MI patients and stroke risk reduction. It merely identifies stroke events as a component of the investigatory endpoints.

Additionally, the Federal Circuit held that a prior art reference that discloses a genus does not inherently disclose all species within that category. *Id.* at 1367 citing *Corning Glass Works v. Sumitomo Elec. U.S.A., Inc.*, 868 F.2d 1241, 1262 (Fed. Cir. 1989) (rejecting as “wholly meritless” an argument that a prior art reference inherently anticipates a claimed species, where the prior art reference disclosed a genus). Similarly, COLCOT contains a genus of at least nine outcome measures, not including the secondary outcome measures relating to total mortality. Of the many outcome measures, only one is stroke. The others include cardiovascular death, resuscitated cardiac arrest, acute myocardial infraction, hospitalization for angina requiring coronary revascularization, deep venous thrombosis, pulmonary embolus, atrial fibrillation, heart failure hospitalization, and coronary revascularization. EX1006 at 2-3. A finding that COLCOT inherently discloses the reduction in the risk of stroke would require that it also inherently discloses the whole group of outcome measures, which is nonsensical. *Id.*

Finally, a finding that a clinical study protocol must render the results that are later obtained inherently anticipated would improperly chill the very research, development, and disclosure the patent system is supposed to incentivize. As Judge Lourie has explained, “[a]n unbounded concept of inherency... threatens to stymie innovation by withdrawing from the realm of patentability that which has not before been known, used, or benefited from.” *In re Montgomery*, 677F.3d at 1383-84 (J.

Lourie dissenting). It is not disputed that “[t]he keystone of the inherency doctrine is inevitability,” which has been upheld by the Federal Circuit repeatedly. *Id.* at 1384 (citing *Bettcher*, 661 F.3d at 639; *Glaxo*, 52 F.3d at 1047; *Hansgirg v. Kemmer*, 102 F.2d 212, 214 (C.C.P.A. 1939). Aside from the unpredictable outcomes of a clinical trial, such a rule would mean there could never be any patents that claim methods for treatment or treatment outcomes as the protocols must be published years before the studies are completed and a patent can be drafted. That cannot be the law, and if it is there will be a chilling result on research and development and clinical testing for new treatment therapies.

D. Dependent Claims 29 to 36 and 39 are not Anticipated

Ground 2 also must fail for the dependent claims 29-36 and 39. Each of these claims add limitations that are either not described in COLCOT or do not alter the inherency analysis, as they were present in COPS as well, where no reduction in risk of stroke was established.

1. Additional medication claims 29-32 are not anticipated by COLCOT.

Dependent claims 29 to 32 require that the patient was prescribed a medication, antiplatelet agent, aspirin or statin respectively. Although COLCOT disclosed patients receiving these drugs, so did the COPS study in nearly the exact same percentages. *See* EX1006; EX2056. As described above, COLCOT does not disclose a reduction in the risk of stroke according to the claimed treatment regimen.

Additionally, also as described above, such a reduction in the risk of stroke according to the claimed treatment regimen is not inherent because COPS treated patients with a very similar protocol, including the administration of antiplatelet therapy, aspirin, and statins, but did not result in a stroke risk reduction.

2. The patient population limitations of claims 33 and 39 are not anticipated by COLCOT.

Claim 33 requires that the patient has atherosclerotic coronary artery disease. COLCOT does not teach that the patient should have atherosclerotic coronary artery disease anywhere in the document. It is conspicuously missing from inclusion criteria which require the patient to have acute MI within the last 30 days, nor is it something a POSA would “immediately envisage.” *Kennametal, Inc. v. Ingersoll Cutting Tool Co.*, 780 F.3d 1376, 1381-82 (Fed. Cir. 2015).

Even if a POSA would understand COLCOT’s statement regarding a cause of MI, stroke, and peripheral arterial disease as a teaching claim 33’s requirement, as explained above, the risk reduction of stroke is neither disclosed in COLCOT nor is it the inherent result of treating a patient according to claim 33.

Claim 39 also narrows claim 27 to a specific patient population, adult humans. Claim 39 is not anticipated for the same reasons described above regarding claim 27.

3. The dose and frequency limitations of claims 34 and 35 are not anticipated by COLCOT.

Claim 34 and 35 require the colchicine dose to be 0.5 mg and administered once per day, respectively. Those claims are not anticipated by COLCOT for the same reasons as Claim 27.

4. Initiation of treatment limitation of claim 36 is not anticipated by COLCOT.

Claim 36 requires that the administration of colchicine is initiated upon assessment in (a) an emergency department (ED), (b) the hospital, or (c) a medical office setting. COLCOT is silent on an assessment and where such an assessment should take place and therefore, cannot anticipate. *Trintec Indus., Inc.*, 295 F.3d at 1296. Moreover, the portion of the COLCOT protocol that Petitioner and Dr. Ridker rely on for meeting claim 36 is the **exclusion criteria**, the exact patients that **will not** receive colchicine as required in claim 36. *Compare* Paper 1 at 34 and EX1049 at ¶ 139 *with* EX1006 at 5 (describing exclusion criteria).

For the foregoing reasons, Petitioner has not shown that the COLCOT protocol anticipates claims 27, 29-36, and 39, and cannot meet its burden of persuasion to show anticipation.

VI. GROUND 3 – CLAIMS 1 TO 50 ARE NOT OBVIOUS OVER NIDORE, COLCOT, ESC GUIDELINES AND/OR COLCRY

Ground 3 must fail because the prior art references, even in combination, are missing at least four elements from the independent claims, and even more from the

dependent claims, that would not have been obvious to a POSA. The four elements include (1) the surprising discovery that a higher loading dose was not required, which was contrary to conventional wisdom and standard of care at the time, (2) the discovery that there was an optimum time to initiate treatment (TTI), (3) that the optimum TTI is within about 3 days after experiencing an MI and (4) that there was a reduction in the risk of experiencing another cardiovascular event, including stroke, in patients who were treated with the claim method versus those who were not. The only way Petitioner can read Nidorf, COLCOT, ESC Guidelines and COLCRYS alone or in combination to suggest the claimed method of treatment is through improper hindsight and picking and choosing teachings, while ignoring the teachings of the references as a whole.

Moreover, Petitioner fails to sufficiently establish a POSA's motivation to combine the cited references or a reasonable expectation of arriving at the claimed invention if combined. As described below, the ESC Guidelines are so broad that a POSA would not have considered combining such teachings with those of Nidorf or the COLCOT protocol. EX1009; EX1006; EX1007. Additionally, the exceptional unpredictability in the relative art requires substantially more evidence of a motivation to combine and reasonable expectation of success than Petitioner supplies.

Additionally, for the reasons described above in Sec. V.A., Petitioner has failed to meet its burden of production to show that the COLCOT protocol is prior art for anticipation or obviousness. Similarly, Petitioner contends that Tardif 2019 and Bouabdallaoui supply motivation and expectation of success in reducing CV events with low-dose colchicine shortly after MI. However, as explained above (*Supra.* at IV), neither of these references are prior art, because the '063 patent is properly attributed a priority date of November 15, 2019. Even if the Board finds that claims 1-26, 28, and 40-50 must have a November 13, 2020 priority date, both Tardif 2019 and Bouabdallaoui are disclosures by the inventor less than one year before the latest possible priority date, which do not qualify as prior art under 35 U.S.C. § 102(b).

A. Independent Claims 1, 8, and 27

1. Nidorf and COLCOT fail to disclose each limitation of claims 1 and 8, nor render them obvious in view of the prior art.

Independent claim 1 of the '063 patent recites: “[a] method of treating a patient after having a myocardial infarction (MI), the method comprising initiating the administration of colchicine at a daily low dose to the patient within about 3 days of the MI, wherein the colchicine is administered without pre-loading the patient with a high dose of colchicine before the administration at the daily low dose, wherein percutaneous coronary intervention was performed for treating the patient’s MI.” EX1001 at 41:29-36. Similarly, independent claim 8 recites a method of

treating a patient after MI, but not requiring PCI and further limiting “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.” *Id.* at 41:50-60. Petitioner alleges that Nidorf and COLCOT teach all of the limitations of claims 1 and 8 except “within about 3 days of the MI.” Paper 1 at 36. However, for the below reasons, Petitioner is incorrect and cannot meet its burden to show obviousness of independent claims 1 and 8.

Petitioner incorrectly described the scope and content of the prior art by relying on non-prior art references as well as hindsight bias to selectively emphasize portions of the prior art without considering references and the prior art as a whole. Specifically, Petitioner ignores or omits references that teach away from the claimed invention, or fail to disclose a claimed feature, motivation to combine other references, or do not support a reasonable expectation of success. The proper scope of the pertinent prior art is determined from the perspective of a POSA without hindsight with the full scope of art pertaining to “the problem facing those skilled in the art at the time the invention was made.” *Insite Vision Inc. v. Sandoz, Inc.*, 783 F.3d 853, 859 (Fed. Cir. 2015). Rather than applying the correct analysis, Petitioner uses “improper hindsight in the selection of the prior art relevant to obviousness.”

Id. at 859 (citing *Monarch Knitting Mach. Corp. v. Sulzer Morat, GmbH*, 139 F.3d 877, 881 (Fed. Cir. 1998)).

Critically, Petitioner fails to consider the Nidorf reference as a whole. To prevent hindsight bias, a prior art reference should be considered as a whole, which may lessen the impact of a single statement in a prior art reference, because that statement in isolation may unfairly suggest that the prior art teaches something it does not. *See St. Jude Medical, LLC v. Snyders Heart Valve LLC*, 977 F.3d 1232, 1242-43 (Fed. Cir. 2020); *Impax Labs. Inc. v. Lannett Holdings Inc.*, 893 F.3d 1372, 1379-81 (Fed. Cir. 2018) (“[Patentee] is correct that in an obviousness analysis, prior art should be viewed as a whole.”).

Petitioner also fails to show that a POSA without hindsight bias would have been motivated to combine the prior art references with a reasonable expectation of success, particularly in view of the unpredictability in the field of invention. Courts have previously found that discovery of specific treatment methods can be unpredictable. *See, e.g., Pharmacyclics LLC v. Alvogen Pine Brook LLC*, 556 F.Supp.3d 377 (D. Del. 2021). Such a finding is well-aligned with the Supreme Court’s explanation of proper application of “obvious to try” as well as the impact of prior art teaching away from combining certain known elements. *KSR Intern. Co. v. Teleflex Inc.*, 550 U.S. 398, 416, 421 (2007). Relatedly, unpredictability in the art tends to show that a POSA would not have had a reasonable expectation in arriving

at the claimed invention. *See Eli Lilly & Co. v. Teva Pharms. Int'l GmbH*, 8 F.4th 1331, 1338-39 (Fed. Cir. 2021); *Novartis Pharms. Corp. v. West-Ward Pharms. Int'l Ltd.*, 923 F.3d 1051 (Fed. Cir. 2019); *Honeywell Int'l Inc. v. Mexichem Amanco Holding S.A. DE C.V.*, 865 F.3d 1348, 1356 (Fed. Cir. 2017).

a. Scope and content of the prior art: Nidorf and COLCOT Protocol

Here, Petitioner's analysis regarding the scope and content of Nidorf is improperly driven by hindsight and does not consider the reference as a whole, including the recited preferred embodiments. Nidorf describes the LoDoCo trial, which administered 0.5 mg/day colchicine to patients with coronary disease that was clinically stable for at least six months. EX1007 at 18:18-35. A POSA would have recognized that the LoDoCo trial results were of limited value because that study was not placebo controlled. Ardehali Decl. Critically, Nidorf also describes various other embodiments that include different dosage and administration regimens, including a loading dose. *Id.* at 15:59-16:28. But, Petitioner ignores these critical portions of Nidorf even though the document identifies the loading dose method as "a preferred embodiment." *Id.* at 16:8-28.

Indeed, Nidorf teaches away from the "no pre-loading dose" limitation. Nidorf not only discloses a higher loading dose in several portions of the specification, it teaches that using a higher loading dose is preferred. Dr. Ardehali

discusses that at the time of Nidorf, a POSA would have understood a higher loading dose of colchicine should be added prior to low-dose therapy. EX2001 at ¶¶ 36-42.

A POSA reading Nidorf at the time of the invention would have understood that it disclosed investigating the effect of adding 0.5 mg colchicine to **standard therapies**, which at the time would include initiating treatment with a loading dose of colchicine. *Id.* Moreover, even if the Board finds that this is sufficient to show disclosure of no pre-loading dose, a POSA would also understand that this specific portion of Nidorf discloses initiating low-dose colchicine **six months after** MI and standard therapy, which includes drugs that would initiate anti-inflammatory treatment and serve the same purpose as the prior art standard pre-loading dose of colchicine. *Id.*

In fact, Nidorf corroborates Dr. Ardeheli's testimony that a POSA would interpret Nidorf as teaching the use of a higher loading dose. Nidorf states unequivocally that in "a **preferred** embodiment, the amount/concentration of colchicine as used herein can be administered at the first day of administration in a higher dose (concentration/amount) compared to the administration of colchicine at following days(s) of administration (maintenance administration/maintenance dose of administration)." EX1007 at 16:8-28 (further teaching, "Preferably, the composition of the invention is administered with a dose of colchicine of between about 1.0 mg and 2.0 mg at the first day... of administration and the maintenance

dose of colchicine at the following day(s) of administration is between 0.5 mg and 1.0 mg.”).

Even if Nidorf does not teach away from omitting a high loading dose, A POSA would not be motivated to do so or have a reasonable expectation that doing so would effectively treat MI based on Nidorf. Nidorf teaches an alternative dosing regimen, but rather than teaching toward the claimed omission of a loading dose, the alternative also teaches away. Like the preferred regimen, the alternative regimen requires a higher colchicine loading dose followed by a lower maintenance dose. The difference in the alternative regimen compared to the preferred regimen is that it allows for two to ten colchicine free days after administration of the higher loading dose, but before beginning administration of the lower maintenance dose. EX1007 at 16:14-26. Thus, Nidorf explicitly teaches away from omitting a loading dose and encourages a POSA to use a higher loading dose.

Nidorf does not suggest or provide any reason to omit the higher loading dose anywhere. Nidorf’s disclosure of the LoDoCo study does not support a finding that Nidorf teaches a POSA to omit a loading dose. Such an interpretation can only be made in hindsight, as it requires a POSA to completely ignore Nidorf’s multiple explicit unequivocal teachings regarding the preference of a loading dose discussed above. *Impax Labs.*, 893 F.3d at 1379-81 (finding that a prior art reference generally disclosing one of several methods of administration of a drug was not obvious

because reference as a whole would not provide motivation with a reasonable expectation of success). It is only through hindsight that Dr. Ridker can claim that Nidorf suggests not using a loading dose. A POSA reading Nidorf would not ignore its teachings regarding the preference for a higher loading dose, which was the common understanding at the time. The explicitly clear teachings of Nidorf reinforces the need for a higher loading dose and would lead a POSA away from the claims of the '063 patent. The Petition offers no specific reason why one of ordinary skill would omit a higher loading dose. And for good reason, as no such reason existed until Dr. Tardif's invention.

With respect to the dose amount, the Board preliminarily found that Nidorf teaches 0.5 mg dosing. However, Nidorf provides a laundry list of acceptable doses that range from 0.1 mg and 5.0 mg, 0.1 mg and 2.0 mg, 0.1 mg to 1.5 mg, 0.1 mg to 1.0 mg, 0.1 mg to 0.75 mg, 0.1 mg to 0.5 mg, 0.25 mg to 5.0 mg, 0.25 mg to 2.0 mg, 0.25 mg to 1.5 mg, 0.25 mg to 1.0 mg, 0.25 mg to 0.75 mg or 0.25 mg to 0.5 mg. EX1007 at 16:55-17:6. Nowhere does Nidorf teach that the use of 0.5 mg dose is ***preferable***. It provides a single embodiment wherein 0.5 mg dose is administered with respect to the LoDoCo study but does not describe it to be a preferable amount. *Id.* at 17:1-6.

Moreover, as discussed above, a POSA would interpret Nidorf as requiring a higher loading dose. Just a few paragraphs above the disclosure of colchicine doses

in Nidorf's column 16, is the unequivocal disclosure that a higher loading dose of 1.0 mg to 2.0 mg is preferred for the first dose followed by a maintenance dose. *Id.* at 16:23-28. Nidorf is clear that a higher loading dose followed by a lower maintenance dose is "a preferred embodiment." *Id.* at 16:8-15. Another sign that a loading dose is preferred is the inclusion of a dose as high as 5 mg in the range of acceptable doses. This would indicate to a POSA that Nidorf teaches a clear preference to use a higher loading dose followed by lower maintenance doses. *Id.* at 16:55-59. The prior art also corroborates the understanding that a loading dose should be used. EX2001 at ¶¶ 18, 25, 28, 36-40, 44, 56; EX1040; EX2007; EX2005; EX2006; EX2002; EX1020.

In addition to teaching away from and providing no motivation for omitting a loading dose, Nidorf also teaches away from administration of colchicine to patients with MI within about 3 days of experiencing MI. Even Petitioner admits that Nidorf does not disclose colchicine administration within about 3 days of an MI. Paper 1 at 36.

Nidorf emphasizes that patients with coronary disease need to be "clinically stable for at least six months" to be given the dosing regimen of the LoDoCo study. EX1007 at 18:33-34. Thus, the earliest a patient could receive colchicine was six months after their MI, but in patients requiring time to stabilize, the time to initiation is even longer. By definition, this would exclude the requirement of claims 1 and 8

that the colchicine is administered ***within*** three days of the MI. It cannot be disputed that patients who suffered an MI less than 3 days ago are not clinically stable for at least six months. A POSA would immediately recognize that rather than teaching or providing a motivation for administering colchicine early after an MI, Nidorf teaches a POSA to wait six months after the patient has been stabilized.

Petitioner's selection of prior art is wrought with hindsight bias and omits critical teachings that a POSA would consider. Specifically, a POSA would have also known and considered the contradictory teachings in the prior art. As Dr. Ardehali explained in his Declaration (and in Patent Owner's Preliminary Response), a POSA would have known that the standard administration of colchicine included administering a loading dose. EX2001 at ¶¶ 23, 25, 38.

Finally, for the reasons described above in Section V.A., Petitioner has failed to meet its burden to show that the COLCOT protocol is prior art.

- b. There is no motivation to combine the prior art with a reasonable expectation because the art is highly unpredictable.

Because Petitioner improperly analyzed the scope and content of the prior art, Petitioner only analyzed the alleged motivation to initiate treatment “within about 3 days of the MI.” Paper 1 at 38. Accordingly, Petitioner has not met its burden showing that Nidorf teaches excluding the pre-loading dose, that COLCOT is prior

art, or that if COLCOT is prior art, that all claim elements were taught in the prior art and provide a POSA motivation to combine those teachings.

Petitioner, and their expert Dr. Ridker, also insufficiently allege that a “POSA would have... been motivated to shorten Nidorf’s treatment initiation time to around 2-3 days post-MI.” The alleged bases that Petitioner relies upon are driven by hindsight bias and do not hold up to scrutiny. Specifically, Petitioner alleges that there was a motivation through (1) routine optimization of 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.” Paper 1 at 38. Petitioner is incorrect on both accounts, and additionally, Petitioner omits critical teachings away in the prior art.

(1) Surprisingly discovering the benefit of early treatment initiation was not a matter of routinely optimizing COLCOT’s 30-day window.

Petitioner again provides only conclusory argument to support its allegation that it would have been a matter of routine optimization to arrive at the “within about 3 days of the MI” limitation from the COLCOT protocol’s 30-day window. The Supreme Court did not mince words explaining that obviousness “cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness.” *KSR*, 550 U.S. at 418 (quoting *In re Kahn*, 441 F.3d 977, 988 (Fed.

Cir. 2006)). Petitioner’s quote from the Federal Circuit misinterprets an explanation of what has occurred in limited circumstances for a legal standard, but that is incorrect. At most, “[a] *prima facie* case of obviousness typically exists when the ranges of a claimed composition overlap the ranges disclosed in the prior art.” *In re Peterson*, 315 F.3d 1325, 1329 (Fed. Cir. 2003). Here, a *prima facie* case is not presumed because Petitioner has not met its burden of production that the COLCOT protocol is prior art and unlike the case of *Peterson*, *Galderma*, and *DuPont*, the claims at issue here cover a method of treatment rather than a composition. *Compare id.*; *Galderma Lab’ys, L.P. v. Tolmar, Inc.*, 737 F.3d 731 (Fed. Cir. 2013); *E.I. DuPont de Nemours & Co. v. Synvina C.V.*, 904 F.3d 996, 1006 (Fed. Cir. 2018) with EX1001 at claims 1, 8.

The distinction between the obviousness analysis in those composition cases and method of treatment claims was made explicit by the Federal Circuit in *Novartis*. In *Novartis*, the Federal Circuit explained that “[t]o the extent the district court required a showing that a [POSA] would have selected everolimus over other prior art compounds, it erred. The proper inquiry is whether a [POSA] would have been motivated to modify the prior art [to arrive at the claimed method of treatment.” *Novartis Pharms.*, 923 F.3d at 1060 (distinguishing overlapping limitation obviousness analysis in method claims compared to composition claims). Accordingly, Petitioner’s conclusory allegations regarding “optimizing” the

COLCOT protocol fails to provide any reason as to why a POSA would have been motivated to arrive at initiating treatment within three days of MI.

- (2) *A POSA would not have been motivated by ESC Guidelines for colchicine regimen, including in view of other prior art.*

Petitioner alleges that the ESC Guidelines and other prior art would have motivated a POSA to initiate colchicine treatment in post-MI patients prior or immediately after hospital discharge. Petitioner bases its allegations on the general teachings of initiating secondary treatments from the ESC Guidelines and other prior art. Petitioner's reliance on Stenestrand and Tran is misplaced because neither investigates when a POSA would initiate treatment with colchicine. EX1008 (investigating early statin treatments); EX1011 (investigating early discharge of MI patients). Although the Deftereos reference discloses administering colchicine early after PCI, the positive outcome is limited to reducing the risk of neointimal hyperplasia and a decreased ISR rate in diabetic patients. *See* EX2064. Moreover, Deftereos's results are also limited to PCI with bare metal stents, which is a differentiation from the findings of O'Keefe. *Id.* However, Petitioner entirely omits the more relevant prior art that taught away from initiating colchicine treatment so soon after MI specifically, as well as after acute CV events.

Petitioner and their expert, Dr. Ridker, also rely on three clinical trials that had no publicly posted results by the November 15, 2019, or even by the latest

possible priority date of November 13, 2020. EX2071 at 183:16-186:2, 186:4-187:9, 187:12-188:13. Unvalidated clinical trial protocols would not provide a POSA with a motivation to follow those protocols, because they are merely hypotheses, particularly in view of the voluminous relevant completed research that can more fully inform a POSA.

A POSA would have been aware of prior art references more specifically directed to colchicine treatments with reported results. O’Keefe appears to be the first publication regarding a study for using colchicine to treat cardiovascular disorders. O’Keefe investigated whether low-dose colchicine initiated within twenty-four hours of coronary angioplasty prevented restenosis post-angioplasty compared to placebo. EX2009 at 2. O’Keefe concluded that low-dose colchicine initiated within one day of coronary angioplasty “proved ineffective in preventing restenosis after coronary angioplasty.” *Id.* at 4. More recently, Raju, which was co-authored by Dr. Nidorf, investigated the effect of colchicine in patients with ACS and acute stroke. EX2054 at 1. The patients in the study were initiated on low-dose colchicine that presented to the hospital with ACS or acute stroke. *Id.* at 2. The study found “no evidence that colchicine 1 mg daily for 30 days compared with placebo suppresses inflammation in patients with [ACS] or acute ischemic stroke.” *Id.* at 1.

Other prior art studies also specifically investigated initiation of low-dose colchicine after MI. Petitioner themselves rely on the Hennessy prior art in their obviousness analyses, however, Hennessy reporting on LoDoCo-MI did not meet its endpoint. The patients in Hennessy were initiated on low-dose colchicine upon admission for acute MI, but patients were excluded if the MI occurred more than 7 days prior initiation. EX1028 at 2. The researchers hypothesized that colchicine would reduce CRP levels < 2 mg/L and thereby indicate a reduction in risk of recurrent CV events. *Id.* at 1. However, a POSA would have understood from the study that in fact the low-dose colchicine “was not associated with a significantly increased likelihood of achieving a CRP level > 2 mg/L or lower absolute levels of CRP 30 days after acute MI.” *Id.* Thereafter, researchers in France conducted the COLIN study. EX2055. The COLIN study investigated the effect of low-dose colchicine administered to patients with an acute MI that underwent PCI for treatment and initiated the colchicine “on the first day of the AMI and for one month.” *Id.* at 3. The study found no effect of colchicine on inflammation as compared to placebo. *Id.* at 2. The authors provide several hypotheses for why the study did not reach its endpoint, including the lack of a loading dose. *Id.* at 7.

Accordingly, a POSA at the time of invention for the '063 patent, would have understood that several prior art references using colchicine for the treatment of CV events and prevention that were initiated shortly after an acute event were found

ineffective. Moreover, a POSA would have understood that the LoDoCo study reported in Nidorf had produced positive results, but in contrast to the other studies the researchers there had initiated treatment after patients were stable for six months. EX2001 at ¶39. Thus, a POSA would not have been motivated to shorten the time after MI to initiate colchicine treatment, but instead would have sought to extend such time.

- c. A POSA would not have reasonably expected initiating colchicine treatment within about 3 days post-MI would reduce risk of CV events.

A POSA would not have reasonably expected that initiating low-dose colchicine treatment within about 3 days post-MI would be effective at reducing the risk of a future CV event compared to placebo. A POSA would not have relied on the teachings of LoDoCo disclosed in Nidorf and the CANTOS study to reasonably expect that the treatment regimen recited in claims 1 and 8 of the '063 patent would be effective.

Petitioner and their expert, Dr. Ridker, again here improperly employ hindsight bias, conclusory analysis, and omission of key prior art to reach the incorrect conclusion of a reasonable expectation of success. Such a flawed analysis does not, and the facts cannot, establish that a POSA would have had a reasonable expectation of success in reducing CV events according to the '063 patent. Under Petitioner's analysis, a POSA allegedly would take the reduced CV events of

patients stabilized for six months from Nidorf and would have applied the treatment initiation of CANTOS (studying a completely different agent), COLCOT (not disclosing any study results), and Deftereos 2013 (studying restenosis recurrence of bare-metal stent PCI treatment in diabetic patients) to conclude “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 [CV] risks...” Paper 1 at 43. Such a path is fraught with impermissible hindsight and ignores multiple more relevant colchicine treatment studies.

As described above, a POSA would have considered other more relevant publications in forming a reasonable expectation of success, including, O’Keefe, Raju, Hennessy, and Akodad. Each of those studies failed to meet their endpoint with low-dose colchicine initiated earlier than the LoDoCo study. Here Petitioner’s bare conclusory statements with a lack of any justification for why a POSA would have the alleged reasonable expectation is insufficient. Indeed, the Federal Circuit has held that it is not enough to merely show a motivation to combine references to establish a reasonable expectation of success. *Eli Lilly*, 8 F.4th at 1344. Additionally, the Federal Circuit found that the Board in *Lilly* did not impose an erroneously high standard of proof requiring the patent challenger to introduce prior art evidence that disclosed efficacy data. *Id.*

Moreover, Petitioner's reasonable expectation analysis ignores the combination of the claim limitation that led to the surprising discovery of Dr. Tardif. For example, Petitioner assesses the reasonable expectation only of treating CV events by initiating colchicine within three days, ignoring other critical limitations. However, the prior art would have also taught away from the claimed invention, for example, Akodad concluding that the lack of a loading dose may have driven the lack of meeting the endpoint. EX2055 at 7.

Finally, because all claims are entitled to the November 15, 2019 priority date, Tardif 2019 and Bouabdalloui are irrelevant to the reasonable expectation of success analysis. For the foregoing reasons, Petitioner has not, and cannot, show that claims 1 and 8 of the '063 patent are obvious over Nidorf in view of COLCOT Protocol, ESC Guidelines, and COLCRYST. Petitioner's analysis is substantially flawed by impermissible hindsight bias, failing to analyze what references teach as a whole, and omitting key and highly relevant prior art from the analysis.

2. Petitioner fails to meet its burden to establish that claim 27 is obvious over the prior art.

Petitioner alleges that claim 27 would have been obvious to a POSA over Nidorf in view of COLCOT and ESC Guidelines, however, Petitioner's analysis again relies on hindsight and remains flawed. As explained above, the preamble of claim 27 is properly limiting, and the claim must require efficacy, or it is

meaningless. Nonetheless, the prior art does not render claim 27 obvious with the efficacy requirement included.

Petitioner alleges that a POSA would understand that Nidorf recites the reducing the risk of stroke limitation, however Petitioner views Nidorf with hindsight in order to meet this limitation. Critically, as explained above, a POSA would understand that Nidorf taught administration of colchicine no earlier than after a patient was stable for six months following MI. EX2001 at ¶39. Accordingly, although Nidorf disclosed an improvement in reduction of risk of stroke in a small sub-set of patients, a POSA would understand that there is a substantial difference between initiating a treatment after a patient is stable for six months compared to within 30 days of an MI. *Id.* Additionally, for the reasons described above in response to Ground 2, the reducing the risk of stroke limitation is not inherently disclosed by COLCOT Protocol.

Relatedly, although the COLCOT Protocol discloses administering low-dose colchicine to patients within about 30 days of MI, the combination of limitations of claim 27 is not taught by COLCOT Protocol. Critically, there is no teaching that such an administration would reduce the risk of stroke.

Petitioner's additional reliance on Nidorf 2013 and CANTOS is also misplaced. Nidorf 2013 reports the results of the LoDoCo trial, which are also described in Nidorf. EX1006; EX1020. As explained above, a POSA would have

recognized that Nidorf 2013 is a substantially different teaching, because the patients in that study were stabilized for six months before treatment initiation, thus a majority of their acute inflammation would have been addressed. EX2001 at ¶ 39. Moreover, a POSA would also understand that the stroke incidence was a significantly small number of total events, limiting its broader applicability, as well as the fact that the LoDoCo study was open label, which increases the risk of bias. As described above, the CANTOS study provided a proof of concept for a treatment pathway, however, that study investigated an entirely different agent. The relevant art for the '063 patent is a highly unpredictable field and the applicability of one agent is not readily translatable to the applicability of another agent. *Supra.* at II.A. Indeed, the predictability or accuracy of the inflammatory hypothesis from CANTOS is not definite, as the treatment of the inflammatory pathway has been shown in some instances to be ineffective. *See, e.g.,* EX2060; EX2061; EX2062; EX2063.

Because of the unpredictability, a POSA would not have been motivated to combine the teachings of CANTOS and Nidorf, nor would a POSA have had a reasonable expectation of success if she did in fact combine those teachings. Accordingly, LoDoCo clinical data, in view of the ***hypothesized*** mechanism of action described in CANTOS, would ***not*** support a motivation and expectation that

0.5 mg/day colchicine treatment initiated within 30 days post-MI would reduce the risk of stroke.

For these reasons, claim 27 would not have been obvious to a POSA over Nidorf in view of the COLCOT Protocol and ESC Guidelines.

B. The Dependent Claims of the '063 Patent Are Not Obvious Under Ground 3

The dependent claims of the '063 patent add limitations to the nonobvious independent claims based upon surprising discovery of Dr. Tardif regarding colchicine treatment regimens. The features were either not disclosed in the prior art and/or a POSA would not have had a motivation to combine the teachings with a reasonable expectation of success. Petitioner's conclusory and hindsight driven analysis falls far short of their burden of persuasion.

1. The CV event reduction claims would not have been obvious in view of the prior art.

Claims 6-7, 9-11, and 50 narrow independent claims 1 or 8, respectively, and recite a reduction in the risk of specific CV events. Petitioner's conclusion of obviousness of these claims is based on hindsight bias and neglects the combinations of limitations rendering the invention patentable.

For example, Petitioner alleges that Nidorf discloses each of these additional limitations, however Nidorf merely taught reduction of CV events with the treatment regimen disclosed in the LoDoCo trial, which specifically required patients to be

stable for six months after an MI before initiating treatment. The condition of a patient stable for six months as compared to a patient within three days of an MI is substantially different. *See, e.g.*, EX2071 at 59:13-20; EX2001 at ¶¶ 39, 47. Therefore, even though Nidorf taught reducing the recited CV events with colchicine treatment, a POSA would have recognized the substantially new and nonobvious regimen recited in the '063 patent that surprisingly and unexpectedly resulted in similar CV event prevention as the LoDoCo trial.

Additionally, for the reasons described above, a POSA would have not been motivated to initiate treatment earlier from the ESC Guidelines, nor from CANTOS. A POSA also would not have had a reasonable expectation of success even if those references were combined, because the more relevant art taught that colchicine initiated shortly after acute CV event, and without a loading dose, was not effective at reducing recurrence of CV events. *See, e.g.*, EX2009; EX2054; EX1028; EX2055.

Finally, contrary to Petitioner's baseless allegation, Bouabdallaoui is not prior art for the reasons explained above. Additionally, Petitioner's reliance on Bouabdallaoui in Ground 3 is misplaced as it is not recited as a combination reference under Ground 3, but only to Ground 4. The claims are also not invalid for obviousness over Bouabdallaoui for the reasons discussed below.

2. The additional medication claims are not obvious over the asserted prior art.

Petitioner further alleges that Nidorf and the COLCOT Protocol teach the limitations disclosed in claims 2-5, 29-32, and 40-43. In Nidorf and COLCOT, the patients received additional medications, including standard secondary prevention therapies such as aspirin, statins, and antiplatelet agents. However, adding the claimed colchicine treatment regimen to these standard secondary prevention agents surprisingly and unexpectedly prevented future CV events. For the reasons described above, such a treatment regimen is nonobvious and for the same reasons, adding the standard secondary prevention therapies is also nonobvious.

3. Patient population claims are not obvious over the prior art references.

Claims 12, 33, and 44 narrow their respective independent claims by narrowing the patient population to “the patient has atherosclerotic coronary artery disease.” Claims 26, 39, and 49 recite treating “an adult human.” Because both of these limitations are in addition to the limitations recited in the independent claims 1, 8, and 27, these claims are also not obvious for the same reasons as those independent claims.

4. Claims 13, 36, and 46 initiation requirements are not obvious

Each of claims 13, 36, and 46 narrow the independent claims with recitation of the administration of colchicine being initiated upon assessment. Each of these claims is not obvious for the same reasons as the independent claims. More

specifically, these claims are nonobvious, because the prior art did not disclose treating or preventing CV events with low-dose colchicine in the claimed time recited by each of these claims. To the extent such a regimen exists in the prior art, a POSA would not have been motivated or had a reasonable expectation of success in combining those references, as explained above.

5. Claims 17-25, 34-35, and 45's dose and frequency limitations are not obvious

Claims 17-25, 34-35, and 45 recite the dosage and frequency of administration according to the '063 patent. Because these claims also include all the limitations of their respective independent claims, they are nonobvious for the same reasons described above regarding the independent claims.

6. Claims 14-16, 37-38, and 47-48 are not obvious

Claims 14-16, 37-38, and 47-48 narrow independent claims 1, 8, and 27 by specifying the form of colchicine and the specific form of the tablet. These claims incorporate all the limitations of their respective independent claims. Because the independent claims are nonobvious, as explained above, so too are these claims.

7. It was not obvious of the prior art to initiate treatment within 4 to 7 days of MI

Petitioner again relies on an erroneous legal analysis and hindsight bias to conclude that claim 28 is obvious. However, as explained above, because administration within about 3 days of MI and about 30 days of MI is nonobvious, so too is administration within 4 to 7 days of MI. Moreover, rather than applying

Galderma and *Dupont*, the Board should apply the rationale of *Novartis* to this case. See *Novartis*, 923 F.3d at 1060. Based upon the correct legal principles, and the prior art references that taught away from initiating treatment so shortly after MI, a POSA would not have found it obvious to initiate low dose colchicine treatment within 4 to 7 days of MI. *Supra.* at VI.A.2.

VII. GROUND 4: CLAIMS 1-26, 28, AND 40-50 ARE NOT OBVIOUS OVER BOUABDALLAOUI IN VIEW OF COLCRYS

For the same reasons discussed in Section IV, Bouabdallaoui is not prior art. Because Bouabdallaoui is not prior art, it cannot anticipate these claims, nor can it be relied on to establish obviousness. The COLCRYS reference only discloses the use of colchicine for gout and FMF. COLCRYS alone or in combination with the general knowledge of a POSA at the time of the invention would not render obvious the method of treating cardiovascular disease, let alone the novel methods claimed in the '063 patent. Accordingly, the Board should find that Petitioner has failed to meet its burden regarding Ground 4.

VIII. OBJECTIVE INDICIA SUPPORT NONOBVIOUSNESS

Dr. Tardif's surprising discoveries from the COLCOT trial and claimed in the '063 patent are novel and nonobvious, as explained above, but substantial evidence of objective indicia also support a conclusion of patentability. The ability to treat CV events and prevent future CV events with the claimed treatment regimen is an unexpected result. Additionally, there was skepticism in the field that initiating a

low-dose colchicine regimen without a loading dose would be effective compared to placebo.

A. The Treatment Regimen(s) Claimed by the '063 Patent Unexpectedly Reduces the Risk of CV Events

At the time of the invention claimed in the '063 patent, November 2019, a POSA would have expected that low-dose colchicine, without a pre-loading dose, initiated shortly after an acute MI would **not** be more effective at preventing future CV events as compared to placebo. However, that is precisely what the '063 patent teaches and was reported in the Bouabdallaoui reference, which discusses the same analysis as that recited in the '063 patent. Evidence showing that a “claimed invention exhibits some superior property or advantage that a person of ordinary skill in the art would have found surprising or unexpected” is indicative of nonobviousness. *Procter & Gamble Co. v. TevaPharm. USA, Inc.*, 566 F.3d 989, 994(Fed. Cir. 2009). The “basic principle behind this rule is straightforward—that which would have been surprising to a person of ordinary skill in a particular art would not have been obvious. The principle applies most often to the less predictable fields, such as chemistry, where minor changes ... may yield substantially different results.” *In re Soni*, 54 F.3d 746, 750 (Fed. Cir. 1995). The Federal Circuit has “repeatedly emphasized” that unexpected results “constitute[] independent evidence of nonobviousness.” *Süd-Chemie, Inc. v. Multisorb Techs., Inc.*, 554 F.3d 1001, 1008 (Fed. Cir. 2009).

At the time of the invention several studies had been done that investigated the usefulness of colchicine to reduce inflammation and treat or prevent CV events. Only the LoDoCo study, which is described in Nidorf 2013 and Nidorf, showed a benefit in low-dose colchicine treatment, however, that treatment regimen was not initiated until ***six months after*** a patient had been stabilized. *See* EX1007; EX1020. Other studies investigated use of low-dose colchicine in the more acute settings, and none of which showed any improvement as compared to placebo. EX2072 at ¶¶ 12-17, 34-36. Indeed, it was reported that “[t]he lack of effect of colchicine in our study could be explained by late administration in the [ICU] after reperfusion and without loading dose.” EX2055.

Unexpectedly, Dr. Tardif discovered that the regimen recited in the '063 patent resulted in a “significant reduction in the incidence of the primary endpoint for patients in whom colchicine was initiated < Day 3 compared with placebo.” EX1006 at 1. This groundbreaking discovery was a substantial departure from what was found in other colchicine studies, despite extensive knowledge of colchicine’s anti-inflammatory effects, and inflammation’s role in recurrent CV events. EX2072 at ¶¶ 33-36. This result is also a benefit over traditional therapies, which were included in the comparator placebo arm of COLCOT. *Id.* The treatment regimen disclosed in the '063 patent resulted in a risk reduction of 23% for ischaemic CV events in post-MI patients. *Id.*

For these reasons, a POSA would recognize that the unexpected result of the treatment regimen claimed by the '063 patent shows the nonobviousness of the claims.

B. The Teachings in the Prior Art Would Have Made a POSA Skeptical

The prior art teachings from 1992 until the invention of the '063 patent in November 2019 overwhelmingly showed that initiation of low-dose colchicine in the acute setting was not effective for treating or preventing CV events. “If industry participants or skilled artisans are skeptical about whether or how a problem could be solved or the workability of the claimed solution, it favors non-obviousness.” *WBIP, LLC v. Kohler Co.*, 829 F.3d 1317, 1335-36 (Fed. Cir. 2016). Accordingly, evidence that those in the industry were skeptical that the claimed invention would work is indicative of nonobviousness because it would have been unobvious to apply teaching contrary to the art. *Kinetic Concepts, Inc. v. Smith & Nephew, Inc.*, 688 F.3d 1342, 1367 (Fed. Cir. 2012).

A POSA would have understood that the prior art taught: (1) inflammation and risk of CV events appear correlated; (2) colchicine can reduce inflammation; (3) colchicine was shown to reduce CV events in one prior art study when initiated in patients that were stable for six months; and (4) the literature repeatedly showed that patients initiated on colchicine in the acute setting received no benefit from the colchicine administration. EX2072 at ¶ 37. From these teachings, a POSA would

have been skeptical that initiating low-dose colchicine, without a pre-loading dose, to patients within 3 days of an MI would reduce the risk of any CV events, including stroke. *Id.* However, Dr. Tardif surprisingly discovered from the COLCOT study results, that patients following his novel treatment regimen did indeed receive the benefit of a reduced risk of recurrent CV event. *Id.* Thus, Dr. Tardif subsequently patented his invention, which resulted the '063 patent.

Because a POSA would have been skeptical that Dr. Tardif's colchicine treatment regimen would work as claimed in the '063 patent, further supports nonobviousness of the claims.

IX. MANDATORY NOTICES UNDER 37 C.F.R. § 42.8

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

Institut de Cardiologie de Montréal ("MHI") is the assignee and owner of the entire title and interest in the '063 patent and the real party-in-interest in this proceeding. Pharmascience Inc. is the exclusive licensee of the '063 patent and is also a real party-in-interest.

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

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

Pursuant to 37 C.F.R. § 42.24(b)(1), the foregoing PATENT OWNER'S RESPONSE contains 13,976 words, excluding parts of this Response exempted under § 42.24(a), as measured by the word-count feature of Microsoft Word.

Dated: April 9, 2024

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