

USPTO

BEFORE THE PTAB

MURRAY & POOLE ENTERPRISES LTD.,
Petitioner

v.

INSTITUT DE CARDIOLOGIE DE MONTREAL,
Patent Owner

IPR2023-01064
Patent 11,400,063

REPLY

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I. INTRODUCTION

MHI has not met its burden to produce evidence corroborating Tardif's sole-inventorship assertion. Rather, "within about 3 days" TTI (time-to-treatment initiation) was derived during brainstorming sessions attended by Bouabdallaoui and others. For that reason and because the '865 provisional (EX1004) does not support that limitation, EX1005 is prior art, and grounds 1 and 4 succeed.

The COLCOT Protocol (EX1006) has been proven to be prior art despite MHI's meritless *ad hominem* attacks against librarian Cruitt. EX1006 undisputedly discloses all active-step claim limitations. Stroke-reduction preamble language deserves no weight because the claim body is complete and does not need the preamble for antecedent basis and because the preamble was not relied on during prosecution. Besides, EX1006 inherently discloses stroke reduction. As a result ground 2 succeeds.

Ground 3 also succeeds because the Nidorf (EX1007) teaches all claim limitations except 0-3 day TTI, which is suggested by other references, with multiple independent rationales to reach that TTI, including, *inter alia*, routine optimization and motivation to begin known effective treatment in the hospital to improve patient compliance with that treatment. A POSA guided by the most germane studies – large-population clinical-end-point studies – would have reasonably expected earlier TTI to be successful. MHI's claims assertions of unexpected results and overcoming

skepticism lack data-based evidence. As cogently explained already and not refuted, the faulty subgroup analysis in EX1005 does not support EX1005's conclusion that 0-3 day TTI is better, a conclusion that defies biological plausibility.

II. GROUNDS 1 AND 4

Grounds 1 and 4 establish that all claims except 27 and 29-39 are either anticipated by EX1005 or obvious over EX1005 in view of COLCRY5 (EX1016). MHI argues only that EX1005 is not prior art. *See* Response (Paper 21) 13-19, 55. Specifically, MHI argues (1) the challenged claims are entitled to the November 2019 priority date of EX1004, *id.* at 14-16, and (2) EX1005 is the work of the inventor, Tardif, *id.* at 16-19. Both arguments fail.

A. No Entitlement to Provisional Filing Date.

The TTI (time-to-treatment initiation) limitations of claims 1, 8, and 28 (“initiating the administration of colchicine ... within ... days of the MI”) are not described in EX1004. Instead, EX1004 discloses “administering colchicine within 5, 10, 15, 20, or 25 days of the MI.” EX1004, 2:32-33; EX2067, 1. Within 5 days is not the same as “within about 3 days” (claims 1 and 8) or “within 4 to 7 days” (claim 28), as the Board correctly realized. *Inst. Dec’n* (Paper 9, “ID”) 50-51.

It is not sufficient that EX1004 discloses longer time spans that *encompass* the recited TTI limitations, as the Board correctly recognized. *ID* at 51. Disclosure

of a broad range is insufficient to support a subrange unless there are blaze marks pointing to the subrange. *See, e.g., In re Baird*, 348 F.2d 974, 982 (CCPA 1965). MHI does not even attempt to identify any such blaze marks in EX1004. Indeed, no one even considered the claimed TTI ranges for “the usual journey of patients with uncomplicated MI” until the later brainstorming meetings that led to the *post hoc* analysis (PHA) of the COLCOT trial data as reported in Bouabdallaoui. EX1005, 4098; EX1077, 37:9-38:6; EX1078, 64:9-65:22, 71:10-72.

MHI’s mischaracterization of Ridker’s testimony as supporting its provisional priority position (Response 16) should be rejected. *See generally* EX1075 ¶¶29-31. First, MHI notes that Ridker admitted that “within 5 days” and “within about 3 days” overlap. *Id.* However, as explained above, merely overlapping is insufficient. Second, MHI misrepresents that Ridker testified that “only the lower limit of stabilization is critical to a POSA.” Response 16 (citing EX2071, 92:1-20). However, he instead said that he puts patients on long-term therapies when they are stable, which may be at day two or three. EX2071, 92:10-20; EX1075 ¶¶29-31. Third, MHI argues Ridker was “unable to articulate the rationale for his opinions” on this issue at his deposition. Response 16. However, Ridker’s rationale is clear in his declaration. EX1049 ¶¶90-96; EX1075 ¶¶29-31. Fourth, MHI argues Ridker applied the wrong legal standard, his testimony is merely attorney argument, and his testimony therefore should be excluded under *Daubert*. *Id.* Those are evidence-

admissibility arguments that are only properly made in a motion to exclude, but MHI has waived that right by not objecting to Ridker's testimony on this basis. 37 C.F.R. § 42.64(b)(1).

B. Claimed TTI Limitations in EX1005 is by Another.

1. Burden Framework

MHI argues that M&P has not met its burden of *persuasion*. Response 18. But, M&P has satisfied its burden of *production*, which has shifted to MHI. *Google LLC v. IPA Techs. Inc.*, 34 F.4th 1081, 1085-86 (Fed. Cir. 2022). The burden-shifting framework of *Dynamic Drinkware* should be applied to this issue with special emphasis on MHI's burden of production because MHI is the sole custodian of all relevant evidence and therefore should be held to a high standard of production, and M&P has no right to discovery here except cross-examination of MHI's chosen witnesses. That is an important difference compared to *Dynamic Drinkware*, which involved a different issue (whether a third-party reference was prior art as of its priority date) where the evidence was equally available to both parties. Uncorroborated, unsubstantiated, non-detailed assertions from the party holding all relevant evidence is inadequate. To hold otherwise would enable every patent owner facing this issue to withhold unfavorable evidence with impunity.

2. Genesis of the Claimed TTI Limitations

It is important not to conflate the COLCOT trial itself with the PHA of later-identified subgroups, including those expressed in the TTI claim limitations. The trial was conducted 2015-2019 and reported in EX1022, whereas the PHA began in late 2019 and was reported in EX1005 in 2020. EX1022, 2500. The trial was designed to test whether treatment within **30 days** of an MI was beneficial; the trial was **not** designed or statistically powered to examine the claimed TTI subgroups, which were not derived until after the trial was completed during brainstorming sessions before the PHA was completed. EX2011 ¶16; EX1077, 37:9-38:6, 51:4-11; EX1078, 64:9-65:22, 71:10-72:16; EX1066, 2798. To be sure, the TTI limitations were disclosed in neither EX1004, EX1006, or EX1022. See EX1077, 82:8-85:7; EX1078, 55:8-21. Furthermore, the PHA TTIs are commonly used goalposts found in past studies. EX1005, 4094 (citing, *inter alia*, EX1011), 4098.

The Tardif and Bouabdallaoui declarations are glaringly silent as to the conception of the claimed TTI limitations. But, in deposition, Bouabdallaoui revealed that the TTIs behind this and other PHAs of the COLCOT trial data were the products of brainstorming sessions attended by her and others besides Tardif. EX1078, 14:12-17:10, 64:9-65:22, 71:10-72:16. Not only can Bouabdallaoui not corroborate Tardif's assertion that he alone conceived of the claimed TTI limitation, but her account is inconsistent with Tardif's assertion. EX1078, 64:14-20 (“[W]hen

the COLCOT study was published, ... Dr. Tardif suggested to a number of the members of his team to discuss any ideas that can ... come ... from the database. So there were brainstormings, discussions within the team.”), 65:10-22, 66:7-20. Bouabdallaoui’s recollection is the only specific, somewhat detailed, credible account of the origination of the TTI subgroups – an account that is inconsistent with sole inventorship.

Other circumstances also suggest that Bouabdallaoui’s role as an inventor was either unappreciated or suppressed. First, Bouabdallaoui is experienced in conducting PHAs, including time-based PHAs. EX1071. Second, she attended the brainstorming sessions that led to the PHA in EX1005. EX1078, 14:12-17:10, 64:9-65:22, 71:10-72:16. Third, she wrote EX1005. EX1078, 74:8-20. This is strong circumstantial evidence that Bouabdallaoui was at least partially the genesis of the claimed TTI limitations. Fourth, Bouabdallaoui, unlike Tardif, is not an employee of MHI and under no obligation to assign her patent rights to MHI, suggesting a financial motivation for MHI to exclude her from the ’063 Patent. EX1078, 32:16-34:8. Fifth, she was not consulted during the preparation or filing of the ’063 Patent application even though she was referenced in the provisional application by her initials, which were later removed before filing the non-provisional, suggesting an effort to exclude her from the patent. EX1077, 87:10-88:5; EX1078, 89:22-92:8

3. Absence of Corroboration

Tardif's sole-inventorship assertion must be corroborated, as MHI admits. *See* Paper 8 at 2 (referring to “rule of reason” evaluation of corroborating evidence); *see also Kolcraft Enters., Inc. v. Graco Children's Prods., Inc.*, 927 F.3d 1320, 1324 (Fed. Cir. 2019) (requiring “independent” corroboration); *Lockheed Aircraft Corp. v. U.S.*, 553 F.2d 69, 74 (Ct. Cl. 1977) (explaining burden is “heavy one requiring full corroboration by other than the inventor's own self-serving testimony or records.”); *Singh v. Brake*, 317 F.3d 1334, 1341 (Fed. Cir. 2003) (explaining “concern that a party claiming inventorship might be tempted to describe his actions in an unjustifiably self-serving manner in order to obtain a patent or to maintain an existing patent.”). Thus, MHI's contention that EX2011 “satisfies all the requirements for an inventor declaration” is incorrect. Response 17.

MHI's few on-point assertions are uncorroborated and vague. For example, Tardif simply asserts he is the sole inventor. Response 17-18; EX2011 ¶5. However, that is conclusory. He offers no independent proof (*e.g.*, contemporaneous documents) of that assertion and does not identify any circumstances (when, where, etc.) of his alleged conception of those limitations (in fact, he does not address conception at all). He certainly does not address the brainstorming sessions Bouabdallaoui described or the specific claimed TTI limitations.

4. Red Herrings

Rather than providing relevant corroboration and detail, MHI makes arguments and its witnesses make assertions that are irrelevant.

First, MHI argues that Tardif alone conceived of the COLCOT trial and designed its protocol. Response 17; EX2011 ¶¶16-17, 28-29; EX2069 ¶3. However, his design of the COLCOT trial has no bearing on the later brainstorming sessions, the PHA, or the later-conceived TTI claim limitations. EX1078, 64:9-72:16, 81:7-82:11.

Second, MHI argues that Tardif was the principal investigator of the COLCOT trial and details his various activities like securing funding, recruiting other doctors, managing the study, etc. Response 18; EX2011 ¶¶17-18. None of these assertions answers who conceived the claimed TTI limitations.

Third, MHI emphasizes that Tardif was the corresponding author of EX1005. Response 18; EX2011 ¶¶27-28; EX2068 ¶10. This is also irrelevant. Authorship does not equate to inventorship. *Google*, 34 F.4th at 1088 (“coauthorship does not presumptively make a co-author a coinventor.”). Assuming the responsibilities of the corresponding author does not imply that the ideas in the paper were solely his.

Fourth, Tardif says he “instructed Marie-Claude Guertin ... to perform a data analysis at my direction ...” EX2011 ¶20; *id.* ¶28. But that is irrelevant if he alone

did not conceive of the claimed TTI limitations, which instead arose from brainstorming sessions. Instructing statisticians to analyze another's idea does not equal sole inventorship. This is also inconsistent with Bouabdallaoui's recollection that following brainstorming sessions, Tardif would select a topic to be addressed and then the team would ask statisticians to look at the data. EX1078, 72:2-16.

Fifth, Ardehali's so-called "corroboration" of Tardif's role is meaningless. Ardehali has no personal knowledge of what Tardif or Bouabdallaoui or others did to create EX1005. EX1076, 65:9-66:18. Ardehali merely presents his understanding of the general responsibilities of a corresponding author. EX2001 ¶¶30-31. Further, Ardehali does not properly understand the legal criteria for inventorship. EX1076, 59:1-60:4, 61:8-69:15 (believing authorship equals inventorship).

Sixth, Bouabdallaoui's testimony that she does not consider herself to be an inventor of the '063 patent (EX2068 ¶4) is an uninformed lay opinion. Bouabdallaoui does not know the legal standard for inventorship, did not study the claims, and was not consulted about the patent. EX1078, 43:20-44:20

Seventh, Tardif's emphasis on his prosecution "declaration" is misplaced. EX2011 ¶23. That was not a Rule-132 declaration, but a form with a bald statement that "I believe that I am the original inventor *or an original joint inventor* of a claimed invention in the application." EX1002, 338 (emphasis added).

In conclusion, MHI has not satisfied its burden to show that the claimed TTI limitations are entirely attributable to Tardif.

III. GROUND 2

Claims 27, 29-36, and 39 are anticipated by EX1006, which MHI contends is not prior art, would not be relied upon by Ridker, and does not disclose all claim limitations. *See* Response 19-30.

A. EX1006 is Prior Art.

MHI alleges that EX1006 was not publicly accessible prior art, contending that it was published later and questioning the correctness and objectivity of librarian Cruitt. *See id.* at 19-20.

Cruitt explains MHI's misunderstanding in a reply declaration (EX1072). To remove all doubt, another librarian has independently confirmed that EX1006 was publicly accessible by March 2017. EX1073 ¶¶22-29.

Next, MHI argues that EX1006 should be disregarded based on statements by Ridker in deposition. *See* Response 20-21 (noting that he would rely on the full protocol rather than a summary like EX1006); *but see* EX1075 ¶¶32-46 (explaining that mischaracterization). That misses the point, which is *not* which document Ridker would read to fully understand the protocol. All that matters is that EX1006

was publicly accessible prior art that fully and clearly anticipates the challenged claims.

MHI also alleges that Ridker's testimony is "mere attorney argument" because he could not immediately recall EX1006 during his deposition. *Id.* 20; *but see* EX1075 ¶¶35-46. That allegation is immaterial since Ridker competently and persuasively testified what EX1006 is and how it anticipates the challenged claims. *See* EX1049 ¶¶76-79, 123-139.

B. EX1006 Discloses All Claim Limitations.

MHI contends that EX1006 does not disclose certain claim limitations, principally stroke reduction. Response 6-10, 22-30.

First, MHI's expert, Ardehali, admitted EX1006 teaches effective stroke treatment within about 30 days of an MI. EX1076, 119:20-121:8 ("So in COLCOT ... if it is started within the first 30 days ... it would reduce the risk of stroke in patients after MI."). Bouabdallaoui also agreed. EX1078, 60:19-62:8.

Second, MHI argues that the preamble of claim 27 should be limiting. *Id.* 6-10. MHI's arguments do not change the ID's correct analysis that the "body of claim 27 defines a structurally complete invention" and "recitation of 'reducing the risk of a stroke' ... does not result in a difference in the way colchicine is administered." ID 10-12.

MHI attempts to rescue this overbroad, single-active-step, poorly drafted claim by appealing to its so-called “essence” and advocating the “cardinal sin” of importing limitations from the specification. *Id.* 7; *Phillips v. AWH Corp.*, 415 F.3d 1303, 1320 (Fed. Cir. 2005) (en banc).

MHI notes that a preamble is limiting when limitations in the body ... rely upon and derive antecedent basis from the preamble. Response 8 (quotations, citation omitted). However, claim 27’s body stands complete on its own without preamble antecedent basis.

MHI’s reliance on the prosecution history fares no better. Response 8, 10. The examiner immediately allowed claim 29 (granted as claim 27). EX1002, 298, 353. The reasons for allowance repeat the entire claim and give no special prominence to stroke reduction. *Id.* 399. This prosecution does not evince the “*clear* reliance on the preamble during prosecution” required to impart weight to the preamble. *Catalina Mktg. Int’l, Inc. v. Coolsavings.com, Inc.*, 289 F.3d 801, 809 (Fed. Cir. 2002) (emphasis added).

Third, even if the preamble were given weight, stroke reduction is inherent in EX1006. MHI does not dispute that EX1006 discloses the sole active method step. According to the ’063 Patent, that method reduces the risk of stroke, and MHI should be estopped from contending otherwise. Stroke-risk reduction “is an inherent feature

of the treatment method taught in the COLCOT protocol,” as the Board correctly recognized. ID, 28.

For the same reason, MHI’s genus-versus-species argument (Response 27) is unpersuasive since it is immaterial to the inherency issue. EX1006 expressly discloses “stroke” as a “Primary Outcome Measure[.]”

Finally, MHI advances a policy argument not based on the law and relying on a *dissent* as its only support. Response 27-28 (citing *In re Montgomery*, 677 F.3d 1375, 1383-84 (Fed. Cir. 2012) (Lourie, J., dissenting)). The *Montgomery* majority held similar method-of-treatment claims anticipated by a trial protocol, as the Board should do here. *Id.* at 1377-78, 1381 (disclosure of protocol inherently treats or prevents stroke.).

MHI does not make credible arguments for any dependent claims apart from their dependence on claim 27. Response 28-30. The arguments in the petition against those claims are sound. Pet. 32-34 (citing EX1049 ¶¶133-139).

IV. GROUND 3

All claims are obvious over EX1007 in view of EX1006, EX1009, and EX1016. MHI espouses numerous arguments including that all claim elements are not taught, lack of motivation, lack of expectation of success, hindsight

reconstruction, teaching away, and unpredictability. For the reasons below, each of these paper dragons lacks merit.

A. All Claim Limitations Taught Except TTI

1. Daily Low Dose

MHI intimates that Nidorf does not teach “a daily low dose,” as recited in each independent claim. Response 38-39. But, as MHI admits, Nidorf teaches an embodiment with 0.5 mg daily, the same “low dose” as in the ’063 Patent. *Id.* 38; EX1007, 18:1-6. Though the claims never define “low dose,” the single low-dose embodiment in Nidorf suffices. Other embodiments, even preferred embodiments, do not negate that patentability-defeating teaching. *In re Gurley*, 27 F.3d 551, 553 (Fed. Cir. 1994); MPEP § 2123 (collecting cases).

2. Without Preloading

First, MHI’s expert, Ardehali, confirmed that LoDoCo (the subject of EX1007) did not include a loading dose. EX1076, 188:12-19.

Second, MHI described LoDoCo and LoDoCo2 before the Canadian and European regulatory authorities as not including a loading dose. EX1053, 24; EX1074, 8; *see also* EX1051, EX1052.

Third, MHI’s belief that silence regarding a loading dose implies presence of a loading dose is incorrect. Response 35-38. In contrast, Ardehali, Bouabdallaoui,

and Ridker explain that a loading dose would be expressly stated, if it were intended in the context of clinical study. EX1076, 126:9–128:21; EX1078, 58:3-16; EX1075 ¶¶47-49. MHI’s suggestion that silence means a loading dose is possible is a reckless disregard for patient treatment. *Id.* ¶ 49.

Fourth, EX1007 describes embodiments with and without loading dose. EX1007, 16:8-28. Therefore, the claim element is met by EX1007.

3. Efficacy

MHI questions whether the references disclose the efficacy results in certain claims (reduced risk of stroke in claim 27’s preamble and lowered risk of certain cardiovascular events in other claims). Response 31, 49, 51-52. However, that language (1) carries no weight and (2) is expressly or inherently disclosed.

Regarding stroke, *see* § II-B *supra*, which applies equally here. Regarding the other efficacy language, the Board correctly determined these phrases “merely define[] the result of the positively recited method steps.” ID, 13. To the extent MHI argues otherwise, that is inconsistent with the ’063 Patent and MHI should be precluded from advancing such arguments. MHI’s reliance on *Allergan* (Response 11-13) is inapposite because nothing in the prosecution of the ’063 Patent relies on those recited results as a reason for patentability. Instead, the examiner predicated allowance on the no-loading-dose limitation. EX1002, 397.

B. Motivation

A POSA would have been motivated to shorten Nidorf's TTI to within about 3 days post-MI to improve patient outcomes. More specific motivations include, *inter alia*, (1) routine optimization, (2) improved patient compliance, and (3) analogous teachings in the ESC Guidelines (EX1009).

1. Routine Optimization

Reducing EX1006's 30-day window would have been a matter of routine optimization. EX1007 taught the benefits of colchicine for stable MI patients. EX1007. EX1006 taught TTI of colchicine to stable MI patients within 30 days, as did CANTOS. EX1049 ¶39-42. Ardehali and Bouabdallaoui admitted COLCOT patients were stable. EX2001 ¶40 ("[T]he patients in both Nidorf [EX1007] and the COLCOT Protocol [EX1006] involved patients that were stable"); EX1078, 55:7-56:8. EX1007 and EX1006 together and individually would have naturally motivated a POSA to initiate a drug known to benefit stable MI patients as soon as the patient is stable. *See* § I-A *supra* at 2 (quoting Ridker). This is a simple case of routine optimization of a single results-effective variable – a “decades-old legal principle.” *Pfizer Inc. v. Sanofi Pasteur Inc.*, 94 F.4th 1341, 1347 (Fed. Cir. 2024).

Indeed, the '063 Patent itself describes other TTI ranges, including 0-4 days and 0-5 days. EX1001, Tables 4-7. The results for 0-4 days were “statistically significant” and for 0-5 days “nominally statistically significant” according to

Tardif. EX1077, 55:6-56:7. MHI's choice to claim 0-3 days is nothing more than an attempt to more closely align the results with patients' "usual journey" after MI. EX1005, 4094, 4098; *see also* EX1078, 68:13-22 (confirming same).

MHI's only arguments against routine optimization are that (1) EX1006 is not prior art and (2) the doctrine does not apply to method claims. Response 41-43. MHI is wrong. Regarding (1), *see* § II-A *supra*. Regarding (2), skilled artisans routinely optimize result-effective variables in all contexts, and the doctrine has been widely applied to method claims, *e.g.*, *Adapt Pharma Operations Ltd. v. Teva Pharms. USA, Inc.*, 25 F.4th 1354, 1361-62, 1366-69 (Fed. Cir. 2022); *E.I. DuPont de Nemours & Co. v. C.V. Synvina*, 904 F.3d 996, 999 (Fed. Cir. 2018). MHI cites *Novartis*, Response 42-43, but *Novartis* neither addresses routine optimization nor limits it to composition claims.

2. Improving Patient Compliance

A POSA would have been motivated to initiate colchicine treatment before a patient leaves the hospital (*i.e.*, within the 0-3 day TTI) for the well-known benefit of improving the patient's compliance with treatment. Pet. 4, 14-15, 38-39, 41-43, 48, 53; EX1049 ¶¶ 157, 165, 171. The Response does not address this; nor does Ardehali. This undisputed motivation independently supports the obviousness conclusion regardless of EX1009.

In fact, MHI applied the claimed 0-3 day TTI to the COLCOT data, not because it was an innovative realization, but because three days was the well-known and commonly accepted cutoff for hospital discharge according to “the usual journey of patients with MI.” EX1005 at 4094 (citing, *e.g.*, EX1011), 4098; EX1078, 68:13-22. Indeed, EX1011 reports that “a 3-day [length of hospital stay] for patients with an uncomplicated AMI has become increasingly popular in clinical practice.” EX1011 at 400; *accord* EX1049 ¶¶ 83,148. The mere lensing of the COLCOT data through a well-known TTI does not support patentability.

3. ESC Guidelines

EX1009, relating to a similarly-positioned active agent in the treatment of stable MI patients, additionally supports the notion that improved patient compliance would result from in-hospital initiation of treatment. EX1009 33. So does EX1008. EX1008, 430. While the Board suggests that EX1009 is too general and does not relate to colchicine, EX1009 teaches when to treat stable MI patients, a concept directly related to the challenged claims.

Moreover, EX1009 supports the obviousness of the claimed TTI period by analogy. Pet. 15, 38; EX1049 ¶¶ 61, 84, 148, 158-160. MHI criticizes EX1009 as concerning statins, not colchicine. Response 31, 43-46. First, EX1009 was a widely recognized definition of the best-practice standard-of-care treatment of ST-elevation

MI patients, a population encompassed by the COLCOT study, shortly, *i.e.*, within 1-3 days, after MI. EX1049 ¶¶80-84.

Second, like colchicine in COLCOT, statins are common first-line treatments for stable MI, and concepts driving timing of treatment of stable MI patients would be highly relevant regardless of the active agent. TTI for statins and colchicine should therefore be similar. EX1049 ¶¶61, 84, 140-142. Ardehali concurs, stating that stable MI patients “should be on statins ... [and] they should also be on colchicine while they are in the hospital,” indicating that the timing of these two agents should be contemporaneous first-line treatments. EX1076: 48:22-49:15, 161:14-163:19.

Third, the FDA approved the colchicine label similar to statin labels. EX1054, EX1055, EX1057. That is, the authoritative governing body believes those two drugs share common medical indications and contraindications. EX1054, EX1055, EX1057.

C. Reasonable Expectation of Success

MHI argues that a POSA would have had no reasonable expectation of success combining the references. Response 46-48.

MHI mis-frames this issue by assuming that the efficacy language in the claims is limiting. That premise is incorrect. *See* § IV-A-3 *supra*. Because the

claim has only a single active step, all that is required is a reasonable expectation of successfully initiating a daily low dose of colchicine to an MI patient within 0-3 days post-MI.

Assuming *arguendo* more is required, a POSA would have reasonably expected that shortening Nidorf's TTI to the claimed range would have successfully lowered the risk of a cardiovascular event for stable MI patients. First, EX1005 is prior art and it, according to MHI, teaches success for 0-3 days TTI. Second, the state of the art sans EX1005 amply supported a reasonable expectation of success, as fully explained in the petition and by Ridker. Pet. at 42-44; EX1049 ¶¶6, 26-53, 141, 161, 169-171, 197, 199.

MHI counters that the CANTOS study concerned a different agent and that other publications reported no success for early TTI. Response 47. However, CANTOS concerned the same inflammatory pathway, as a POSA would have appreciated, EX1049 ¶¶4-6, 12, 35-37, 47-48. Indeed, Tardif explains that CANTOS is relevant to colchicine use, admitting that CANTOS investigates the same inflammatory pathway and "is cardioprotective" in patients with a previous MI. EX1079, 1838.

Additionally, the other studies cited by MHI do not negate the teachings of the most germane trials – LoDoCo, CANTOS, and COLCOT – that early treatment post-MI would be beneficial. As explained by Ridker, those were the most pertinent

studies because they were long-term clinical end-point studies, not short-term and/or biomarker studies. EX1075 ¶¶7-22.

MHI cites *Lilly* as requiring efficacy data to establish a reasonable likelihood of success. Response at 47. *Lilly* does not support that proposition. “[T]he expectation of success need only be reasonable, not absolute.” *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1364 (Fed. Cir. 2007) (citing *Merck & Co. v. Biocraft Labs., Inc.*, 874 F.2d 804, 809 (Fed. Cir. 1989) and *In re O’Farrell*, 853 F.2d 894, 903 (Fed. Cir. 1988)). In this case, even before the COLCOT results and EX1005, the expectation of success of early TTI was reasonable based on LoDoCo, LoDoCo2, and CANTOS. EX1075 ¶¶7-28.

Finally, MHI argues that the combination of early TTI and no loading dose is especially significant in the reasonable-expectation-of-success analysis. Response 48. However, the prior art, especially LoDoCo, CANTOS, and EX1006, already taught the TTIs and had no loading dose. *See* § IV-A-2 *supra*.

D. No Hindsight, Teaching Away, or Unpredictability

MHI frequently cries “hindsight” but everything except the claimed TTI range is expressly disclosed in Nidorf, and TTI was a readily optimizable result-effective variable, the *prior art* taught motivation to reduce TTI, and the claimed TTI was based on the usual patient journey in the *prior art*. Success in reducing TTI would have been reasonably expected from the most germane *prior-art* references and

studies (LoDoCo, LoDoCo2, and COLCOT). EX1075 ¶¶7-28. No hindsight reconstruction is needed to arrive at the claimed invention.

MHI's teaching-away arguments are limited to the "without preloading" limitation, Response 35, 37-39, or less germane references, *id.* 43, 48, both answered above.

MHI contends that treating cardiovascular disease and stroke is unpredictable. Response 4-6. But the issue here is much narrower: Whether earlier TTI of daily low-dose colchicine to stable post-MI patients would predictably yield benefit. A POSA would have reasonably predicted the answer to be yes at the time of the invention, as explained above. *See* EX1075 ¶¶23-28. "[O]bviousness cannot be avoided simply by a showing of some degree of unpredictability in the art so long as there was a reasonable probability of success." *Pfizer v. Apotex*, 480 F.3d at 1364. "Obviousness does not require absolute predictability." *E.g., O'Farrell*, 853 F.2d at 903.

V. SECONDARY CONSIDERATIONS

MHI asserts two secondary considerations: Unexpected results and skepticism. Response 55-59. A common flaw with both assertions is that MHI's alleged invention (initiated treatment within 3 days, no pre-loading) cannot yet be said to have achieved any results, unexpected or otherwise, and as such the alleged

skepticism has not yet been overcome. The data in EX1005 simply do not support that claim. The '063 Patent premise is built on a cherry-picked interpretation of data.

“[U]nexpected results is a factual, evidentiary inquiry.” *In re Mayne*, 104 F.3d 1339, 1343 (Fed. Cir. 1997); *see also In re Inland Steel Co.*, 265 F.3d 1354, 1365 (Fed. Cir. 2001) (affirming obviousness conclusion where “insufficient data had been presented to prove the unexpectedly favorable results.”).

MHI’s only data proffered in support of unexpected results are in EX1005 (repeated in EX1001 Tables 1-3). However, MHI cannot rely on EX1005 to show unexpected results because it is prior art. *In re Kao*, 639 F.3d 1057, 1069 (Fed. Cir. 2011) (“[T]here must be a nexus to some aspect of the claim not already in the prior art”). Moreover, EX1005 is a subgroup-based PHA that does not statistically support MHI’s unexpected results, as explained by Ridker (EX1049 ¶¶220-248), which MHI has **not** even attempted to **refute**. *See also* Pet. 56-61 (presenting same).

First, the COLCOT study was designed to determine whether a daily low dose of colchicine initiated within 30 days after an MI was beneficial; it was **not** designed to assess outcomes based on the claimed TTI. EX1077, 55;8-21. The 0-3 day subgroup was **not** pre-specified but instead arose from the later brainstorming and subsequent PHA. *Id.*

It is well known that subgroup analyses are notoriously unreliable. As a seminal paper says, “Subgroup analyses in clinical trials [are] fun to look at, but don’t believe them!” EX1067, 1. Famously, a subgroup analysis of a clinical trial that overwhelmingly found aspirin to be an effective cardiovascular treatment, found it to be ineffective in Geminis and Libras when looking at astrological-sign subgroups. *Id.* 2. The paper summarized:

Analysis of subgroup results in a clinical trial is surprisingly unreliable, even in a large trial. This is the result of a combination of reduced statistical power, increased variance and the play of chance. ... When clinicians believe such subgroup analyses, there is a real danger of harm to the individual patient.

Id. 1 (abstract); *accord* EX1068 (“Subgroup analysis and other *(mis)uses* of baseline data in clinical trials” (emphasis added)). Moreover, Tardif concurred with this view. EX1077, 38:21-39:10, 42:3-15, 49:21-50:11. (admitting PHAs are “less strict,” “less stringent,” and “less strong”) (admitting “prespecified” is “better”). Nevertheless, while “prespecified” may be better than PHA, it is still not reliable as evidenced by Tardif’s own COLCOT supplement showing that colchicine worked (1) in men but not women (HR 0.70 vs. 0.99); (2) in patients with no prior MI/stroke but not with prior MI/stroke (HRs 0.68/1.05 without/with prior MI; 0.76/1.09

without/with prior stroke); and (3) in patients without PCI/CABG but not with PCI/CABG (HR 0.72 vs. 0.91). EX1062, Table S3; EX1077, 40:3-49:18.

These are not just generalized concerns. EX1012 is a published paper pointing out these very deficiencies in EX1005 specifically, as explained by Ridker. EX1049 ¶¶234-245; *see also* Pet. 56-57. EX1012 concluded that “a play of chance cannot be distinguished from these data.” EX1012, 4. MHI has **not** addressed EX1012 at all.

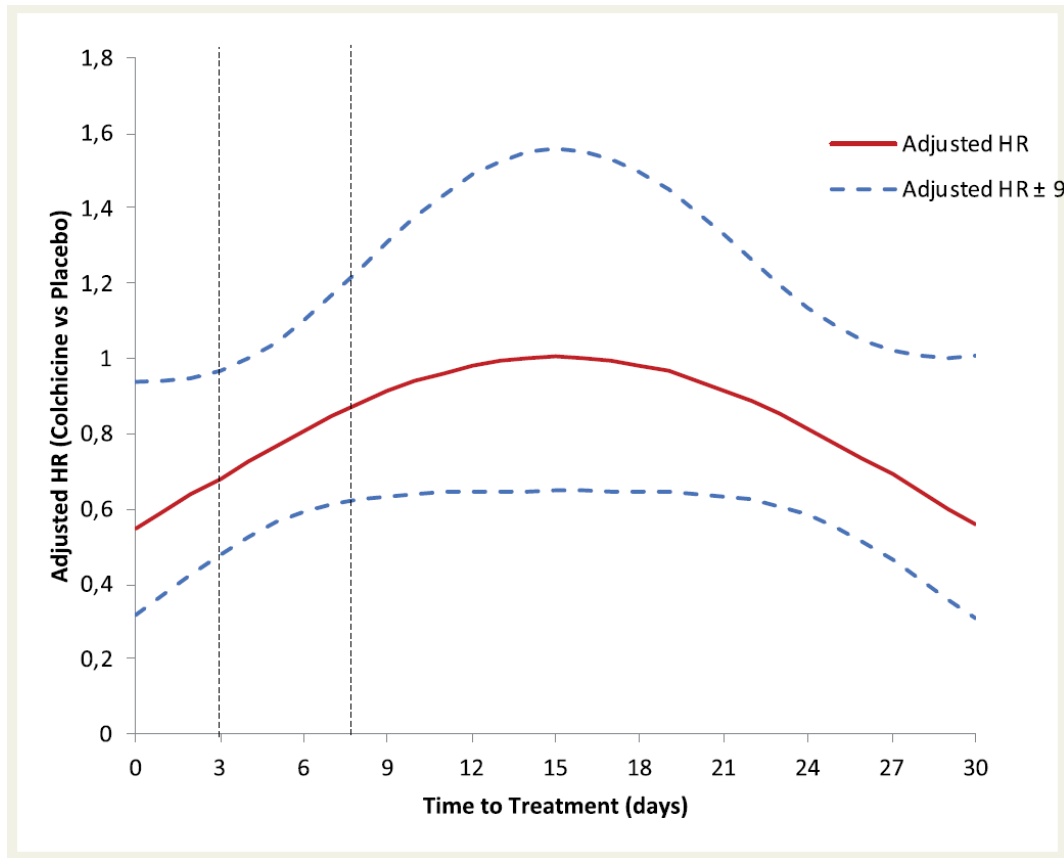
There are numerous specific problems with the PHA described in EX1005. First, comparing hazard ratios (HRs) and p values of different subgroups is not reliable where, as here, interaction p values that assess whether a treatment effect differs ***between the subgroups*** are not provided. EX1012, 3 (“The authors did not report whether the differences in observed effect size between strata were statistically significant”); EX1068, 1069 (“Statistical tests of interaction ... should be used rather than inspection of subgroup p values, which often encourages inappropriate subgroup claims ...”). EX1049 ¶¶226, 240-242.

Second, no breakdown of baseline characteristics for the placebo and colchicine arms in each subgroup were provided, meaning selection bias in the 0-3 day subgroup cannot be ruled out. EX1049 ¶235 (citing EX1012 6, questioning whether the subgroups were “sufficiently randomized” and noting “patients in the

TTI 0-3 day subgroup would be potentially less prone to developing post-MI cardiovascular events independent of colchicine treatment effects”).

Third, there was insufficient statistical power to test the 0-3 day subgroup. In fact, the overall COLCOT study was only statistically powered to test the entire 30-day cohort. EX1060, 26-27 (explaining why “[a] sample size of approximately 4500 randomized patients ... would yield adequate power.”); EX1022, 2504 (Tardif admitting “a larger trial could have allowed a better assessment of individual end points and subgroups ...”).

Fourth, the conclusions of EX1005 defy biological plausibility. Figure 2 (reproduced below) undermines EX1005’s conclusion of a statistically significant benefit for the 0-3 day TTI subgroup. Figure 2 shows the benefit to be just as large when initiated late in the 30-day window as in days 0-3. EX1076, 89:11-90:19; 96:9-98:1. This confirms the overall findings of COLCOT, LoDoCo, and LoDoCo2, none of which showed a difference in benefit across different time periods. EX1077, 60:7-18 (Tardif agreed that administering colchicine at any point within 30 days possibly has a positive effect). Yet, mysteriously, Figure 2 shows diminished benefit, perhaps even harm, for treatment initiated in the middle of the 30-day window. EX1076, 87:2-88:9, 109:15-115:9. There is no biological explanation for this. Biological plausibility is the cornerstone of credibility of subgroup analyses. If a subgroup finding is not “biological[ly] plausib[le],” it is unlikely to be real. EX1068, 1069.



In conclusion, EX1005's PHA suffers from all the known problems of subgroup analyses: the subgroups were *post hoc*, small, not randomized, and statistically underpowered; the purported effect relies on subgroup p values and not on statistical tests of interaction; and it is not biologically plausible that a drug known to be effective long-term would be ineffective when initiated on certain days within the first 30 days. There is no plausible interpretation of MHI's weak PHA data that could support its claims of unexpected results or overcoming skepticism.

As a result, the strong *prima facie* case of obviousness has not been rebutted.

2024 July 12

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CERTIFICATE OF SERVICE

I hereby certify that on July 12, 2024, copies of the foregoing REPLY and all documents filed with it were served via electronic mail to counsel for the patent owner, as consented to by counsel, upon the following counsel for the petitioner:

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