

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 No. IPR2023-01064
U.S. Patent 11,400,063

SECOND DECLARATION OF PAUL RIDKER, M.D.

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I, Paul Ridker, M.D., declare under penalty of perjury as follows:

1. I submit this declaration on behalf of Murray & Poole Enterprises Ltd. (“Murray & Poole”) as a scientific expert in connection with the *inter partes* review (IPR) of U.S. Patent No. 11,400,063 by Tardif (“the ’063 Patent”) in the case identified on the cover page. I have personal knowledge of the facts stated in this declaration and have personally reviewed the documents discussed herein. If called as a witness, I could and would competently testify to such facts under oath.
2. I prepared a declaration (“First Declaration”), which is dated June 14, 2023 and was filed in this case as Exhibit 1049. I reaffirm and incorporate into this, my Second Declaration, the content of my First Declaration.
3. I submit this Second Declaration to add technical details regarding the assertions made by the Patent Owner.
4. Where appropriate, I refer to exhibits that I understand were filed by the parties in this case.
5. I may rely on these and additional materials to respond to arguments raised by the Patent Owner. My review and assessment of the materials provided in this proceeding is ongoing, and I will continue to consider any new material as it is provided. I reserve the right to review, supplement, and amend my analyses based on new information and on my continuing review of the materials already provided.

I. PREDICTABILITY

6. The Patent Owner argues that the field was unpredictable because some studies show that colchicine does not have any effect against cardiovascular disease, whereas other studies show an effect of colchicine in improving clinical outcomes in patients with cardiovascular disease. This is incorrect. At the filing date of the '063 Patent, the field was not unpredictable. Quite to the contrary, colchicine at a dose of 0.5 mg once daily had already been established as a highly effective method to reduce cardiovascular event rates in patients with or at high risk for chronic atherosclerotic disease, as well established in three large scale randomized clinical trials: LoDoCo, LoDoCo2 and COLCOT, the latter two of which were additionally placebo-controlled. These trials were cited by the Patent Owner in their own regulatory filings with the European Medicines Agency (EMA) and the Canadian Agency for Drugs and Technologies in Health (CADTH) as being the most important references to rely on. EX1051-1053, EX1074. By contrast, the studies cited by the Patent Owner as showing unpredictability are uninformative due to either their small sample size, their use of surrogate rather than clinical outcomes, and/or because they were conducted among unstable patients in the setting of acute coronary ischemia where it remains uncertain even today whether low dose colchicine is or is not effective. However, as will be discussed below, none of these show unpredictability for stable patients with atherosclerosis.

A. Classification of the References

7. The Patent Owner asserts in its Response that “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.” Paper 21 at 5. As summarized in the following two paragraphs, these publications fit into two groups.

8. The first group of publications includes those studies, which according to the Patent Owner, found that low-dose colchicine was not effective to treat certain CV events when compared to placebo. *Id.* at 5. These studies include O’Keefe (EX2009), Raju (EX2054), Hennessy (EX1028), Akodad (EX2055), and Tong (EX2056). *Id.*

9. The second group of publications includes those studies, which according to the Patent Owner, found that low-dose colchicine could be effective at treating certain CV events when compared to placebo. *Id.* at 5. These studies include Deftereos 2013 (EX2064), Nidorf 2013 (EX1020), Nidorf 2020 (EX2065), and Tardif 2019 (EX1022).

10. In addition, the Patent Owner cites Shah (EX2066) and Judkins (EX2063) in respect of teaching an effect/no effect of colchicine.

11. The references do not teach what the Patent Owner claims they teach. To make this easier to understand, I have grouped the references below in Table 1 based on the following factors:

- a. whether the primary outcome of the study involved informative data using hard clinical endpoints (such as myocardial infarction, stroke, unstable angina, and cardiovascular death); or whether the study involved less informative data using surrogate endpoints (such as biomarker changes, imaging tests, or tests of coronary flow).
- b. whether the study looked at outcomes in the setting of unstable patients with acute coronary ischemia or whether the study looked at patients with stable chronic coronary artery disease;
- c. whether the study had a large sample size (and is thus clinically meaningful and informative), or had a small sample size (and was thus not necessarily informative relative to the large scale studies).

In my experience, these reflect the factors that are relevant to the question of whether a study can inform about which interventions might have (or do not have) an effect on patient outcomes.

12. In Table 1, the exhibit number is in **bold** for the studies the Patent Owner has asserted as showing that colchicine has an effect on cardiovascular outcomes. The

Patent Owner considers the other studies to show that colchicine does not affect cardiovascular outcomes.

Table 1	
Category	Publications
Clinical endpoints, unstable patients with acute coronary syndrome, intermediate sample size	EX2056
Clinical endpoints, patients with stable atherosclerotic disease, intermediate or large sample size	EX1020 EX1022 EX2065
Surrogate endpoints, unstable patients with acute coronary syndrome or acute stroke, small sample size	EX1028 EX2054 EX2055 EX2066
Surrogate endpoints, stable patients with atherosclerotic disease or undergoing angioplasty, small sample size	EX2063 EX2009 EX2064

13. It is immediately evident from Table 1 that of the four studies considered by the Patent Owner to show that colchicine has an effect on cardiovascular disease, three are hard clinical endpoint trials in stable patients, the moderately sized LoDoCo1 trial (EX1020, sample size 532), the large LoDoCo2 trial (EX2065,

sample size 5,522), and the large COLCOT trial (EX1022, sample size 4745) whose data underlies the '063 Patent. This is fully in agreement with my opinion that these three studies clearly established that low dose colchicine was effective in stable patients with atherosclerotic disease, and that only these three studies are relevant to the expectation of success of the therapy defined in the '063 Patent which is fully limited to stable patients. Since the effectiveness of colchicine in this indication and patient population was already known before the priority date of the '063 Patent, none of the other references cited by the Patent Owner are informative about the therapy in the '063 Patent.

14. It is also immediately evident that those references considered by the Patent Owner to show that colchicine has no effect or is unpredictable, are for the most part studies of far less reliable surrogate endpoints conducted in unstable patients with acute coronary ischemia. This is a very different clinical setting with different biologic needs where it remains even today uncertain as to whether colchicine is or is not effective. However, none of these is pertinent to patients with stable disease, the issue in the '063 Patent. Further, with rare exception, these studies are also of small sample size and are thus simply unable to provide fully informative clinical data. This latter limitation of small sample size is also the case for the studies of more stable patients referred for angioplasty, which are further compounded by the fact that they largely rely on surrogate rather than hard clinical endpoints. As such,

none of these studies is fully informative, particularly in view of the three conclusive clinical outcome studies (LoDoCo, LoDoCo2 and COLCOT) previously showing the effectiveness of colchicine in stable patients with atherosclerotic disease.

B. Only the three hard clinical outcome trials in stable patients with atherosclerotic disease are relevant

15. The '063 Patent is directed to stable patients. The underlying data of the '063 Patent are those of the COLCOT trial, which studied the effect of colchicine on stable atherosclerosis. Each of the three clinical trials highlighted above had already demonstrated the effectiveness of colchicine at 0.5 mg once daily in therapy of stable atherosclerosis: LoDoCo (EX1020), COLCOT (EX1022) and LoDoCo2 (EX2065). These are the only relevant studies for the '063 Patent. COLCOT and LoDoCo2 in particular were “gold standard” clinical trials: they both had a large enough sample size for statistical power; they investigated hard clinical endpoints, rather than surrogate endpoints, and they were both placebo-controlled, multicenter trials. They confirmed the LoDoCo results, which were not placebo-controlled and in a smaller patient cohort, although large enough for statistical power.

16. It was therefore well-established in these three trials that low-dose colchicine was effective in stable atherosclerotic disease, whether treatment was started after being stable for six months or when stable within thirty days of a myocardial infarction.

17. Studies such as EX1028, EX2054, EX2055, EX2056, and EX2066 were conducted in the setting of acute ischemia or acute coronary syndromes, a setting where a very different biology is in play and where it remains uncertain as to whether colchicine is or is not effective. This is, however, irrelevant to the present discussion because COLCOT is a trial in stable patients. The studies in the acute setting are not informative about effectiveness in treating chronic atherosclerosis in stable patients.

18. The studies EX2054, EX2055, EX2063, EX2064 are of insufficient sample size to provide a POSA with either a convincing positive finding or an informative neutral finding capable of overcoming the certainty of effectiveness established by the LoDoCo, COLCOT and LoDoCo2 trials. This is not evidence of controversy from a biologic perspective, it is simply the result of small studies that are less informative compared to the large, hard endpoint clinical trials. With the exception of EX2063, which was conducted in stable patients, these studies overlap entirely with the studies investigating colchicine effectiveness in acute settings.

19. Studies EX2009, EX2054, EX2055, EX2063, EX2064, are not only of small sample size but further are, as well as EX2066 and EX1028, based upon surrogate endpoints as primary outcome (such as change in hsCRP, flow-mediated dilation, or troponin I measurement) that may or may not ultimately prove informative when large hard outcomes trials are conducted. Reliance on surrogate endpoints has a long and often disappointing history in cardiovascular medicine as such endpoints all too

often have failed to predict actual hard clinical endpoints. Moreover, while surrogate endpoint studies might be considered informative under some circumstances (for example, at the time of the EX2063 study, FMD was considered a surrogate that was informative for cardiovascular disease), they are simply irrelevant to the present discussion, given that all parties agree that it is the hard outcomes data from COLCOT that is being discussed, and the effect of low-dose colchicine on hard clinical endpoints was already established by LoDoCo and LoDoCo2. In addition, several of these studies evaluate the impact of colchicine on changes in hsCRP, a surrogate endpoint which has sometimes but by no means always been informative as to whether a given intervention will or will not ultimately prove effective for reducing actual clinical endpoints; in fact, some well-known interventions that lower hsCRP such as steroids are harmful for patients. EX2061, EX2062. Further, as already noted above, none of the surrogate endpoint studies are relevant to the '063 Patent which is based on COLCOT, a hard endpoint trial of stable patients.

20. The Patent Owner cites further exhibits which do not relate to clinical studies at all: EX2057, EX2058, EX2059, EX2060, EX2061, EX2062, EX2073 and EX2074. These are largely reviews, editorials with no new information such as EX2057, or manuscripts describing prediction models many of which such as EX2058, EX2059, EX2060, EX2073, and EX2074 do not address colchicine. They are thus not relevant for determining clinical predictability or unpredictability of

colchicine and are not addressed herein, except to note that EX2061 and EX2062 explain that hsCRP is a biomarker for CV risk, in the sense that an elevated hsCRP indicates elevated risk, but that hsCRP has not proven to be causal in cardiovascular disease, meaning that lowering hsCRP does not in and of itself predict the effectiveness of a given intervention on cardiovascular outcomes. As noted above, the change in hsCRP with a given intervention has sometimes but by no means always been informative as to whether the same intervention will or will not ultimately prove effective for reducing actual clinical endpoints. It is important to understand this, because this is why the biomarker studies cited by the Patent Owner, all of which looked at the effect of colchicine on hsCRP, cannot accurately predict clinical outcomes and cannot show that colchicine does or does not have any effect against cardiovascular disease. Moreover, as also noted above, all of these surrogate endpoints are irrelevant given that the '063 Patent is based on COLCOT, a hard endpoint trial.

21. The Patent Owner cites EX2064 as a fourth study in which colchicine showed an effect. EX2064 investigated restenosis, the recurrent closing off of an artery after insertion of a stent, not myocardial infarction, stroke, or cardiovascular death. This limitation, as well as the small sample size of the study, are clearly discussed by the authors in EX2064 who state: “The endpoints of the present study were not clinical. More powered studies with longer follow-up would be needed to demonstrate a

clinical benefit for colchicine use in this setting. As a result, no firm clinical recommendation can be made on the basis of these findings.” (EX2064, p. 7, LH col., second paragraph). While the EX2064 result showed an effect of colchicine on restenosis, this alternative endpoint was not informative as to the hard clinical endpoints in the ’063 Patent, because the hard clinical endpoint studies EX1020, EX1022 and EX2065 had already established the effect of low dose colchicine in stable atherosclerotic disease.

22. One clinical endpoint study is cited by the Patent Owner as showing unpredictability: EX2056, the COPS trial. However, as described above, the COPS trial (EX2056, Tong 2020) was a study of unstable patients with acute coronary syndrome which is a very different biologic and clinical situation than studies of stable patients, which of course is simply not relevant to the ’063 Patent nor to the patients enrolled in the COLCOT trial.

C. Conclusion Regarding Predictability

23. There was no lack of predictability at the relevant date for the ’063 Patent.

24. The hard clinical endpoint studies in stable patients, EX1020 (LoDoCo), EX1022 (COLCOT), EX2065 (LoDoCo2) show a conclusive effect of colchicine in therapy of cardiovascular disease and prevention of cardiovascular events.

25. EX1020, EX1022 and EX2065 are essentially the same investigations as the '063 Patent: they use the same dose and dosage regimen, in a large cohort of stable patients, and measure the same hard endpoint clinical outcomes over the similar time period. EX1022 and EX2065 in particular were set up with large enough samples to test in a statistically definitive manner the efficacy of low-dose colchicine, and they had the additional strength of being placebo controlled. These three clinical trials are the only relevant ones for the predictability of the effect of colchicine in the '063 Patent. They conclusively answer the question of whether colchicine has an effect on cardiovascular events in the treatment of stable patients with atherosclerosis.

26. The Patent Owner correctly cites these clinical trials as showing that low-dose colchicine is effective at treating certain CV events when compared to placebo. (Paper 21 at 3-5).

27. As further proof, these studies are corroborated by the CANTOS trial results, which proved definitively both the concept and the mechanism of the inflammation hypothesis of atherothrombosis among stable patients.

28. The Patent Owner is incorrect to say that there was a lack of predictability of the results of the '063 Patent. By the priority date (Nov. 15, 2019) there was no doubt that low-dose colchicine is effective at treating and preventing cardiovascular events in stable patients with cardiovascular disease.

II. DEPOSITION QUOTES

A. Quotes Related to Ground 1

29. The Patent Owner falsely represents my deposition testimony about the teachings of the '865 provisional application regarding the range encompassed by “within 5 . . . days of the MI”:

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.

Paper 21 at 15. Below is the section of my transcript of my deposition cited by the Patent Owner.

1 Q Okay. We can -- we can try to simplify,
 2 I suppose. And -- and perhaps your answer of we
 3 don't have a math dispute revolves it.

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

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

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

Ex. 2071 at 92:1–20. Reviewing this section of my deposition transcript makes it clear that I merely indicated responsible physicians put patients on a long-term therapy of using colchicine when a patient is stable without characterizing the range of the '063 Patent as being disclosed by the range in the '865 provisional application as asserted by the Patent Owner.

30. The Patent Owner also falsely represents my deposition testimony regarding the priority date of the '063 Patent. The Patent Owner states:

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.

Paper 21 at 15, 16. Again, reviewing the sections of my deposition transcript, provided below, makes it clear that I merely indicated responsible physicians put patients on a long-term therapy of using colchicine when a patient is stable without characterizing the range of the '063 Patent as being disclosed by the range in the '865 provisional application as asserted by the Patent Owner.

31. Below is the cited section of transcript of my deposition.

1 Q So I'll represent to you that this --
2 Exhibit 4 is a copy of the specification of the
3 November 2019 provisional application, which
4 eventually matured into the '063 patent. So this
5 was the initial filing, which eventually became
6 the '063 patent.

7 A Okay. That's actually very helpful. I
8 appreciate your explaining that.

9 Q Okay. And I specifically want to ask
10 you about page 2 in that last paragraph.

11 And are you there?

12 A I'm -- I'm reading -- it -- it's
13 starting "in some embodiments"?

14 Q Correct.

15 A Okay. Is there a question?

16 Q I can give you the question.

17 And do you see there it says:

18 In some embodiments, the method involves
19 administering colchicine within 5, 10, 15, 20, or
20 25 days of the MI.

21 You see that. Right?

1 Q Okay. And so would a POSA understand
2 that this part, the method, involves administering
3 colchicine within five days of the MI to mean
4 initiating the colchicine within from whatever day
5 the patient is stabilized up until day five?

6 MR. LAURENCE: Objection; form.

7 THE WITNESS: Well, again, I -- I think
8 you're actually drawing the most important
9 distinction, Matt, I -- which I think we can both
10 agree on. These are all stable patients. At
11 whatever time this is done, it's stable. So if
12 it's 5 or 10 or 15 or 20, we all -- we acknowledge
13 these patients are stable.

14 BY MR. WILKERSON:

15 Q I guess, from -- from the position of a
16 POSA, when would they understand that initiating
17 colchicine treatment within five days of the MI to
18 include? What's our kind of lower and upper limit
19 of within five days of the MI for initiating
20 colchicine?

21 MR. LAURENCE: Objection; form.

22 THE WITNESS: This is a chronic therapy

1 that often occurs within, you know, two or three
2 days. And everything else is variable.

3 Q Okay. That's fine. Let's -- let's get
4 a little -- we can be a little -- slightly more
5 pointed, I suppose.

6 So you agree with me that this
7 provisional application discloses initiating --
8 sorry, administering colchicine within five days
9 of the MI. You agree that that's said here?

10 A It's -- yes, it says you can administer
11 within five days, and I'm going to presume that
12 means when the patient is stable, as you have
13 stipulated.

14 Q And then -- so I want to go back, then,
15 to that page 58 of your declaration if we can.

16 A Okay. Hang on.

17 THE WITNESS: (Indiscernible.)

18 MR. LAURENCE: Yep.

19 THE WITNESS: All right. Let's see.

20 Okay.

21 BY MR. WILKERSON:

22 Q And I think I know your answer to this,

1 but we're going to ask it anyway.

2 Is it your opinion that within five days
3 of the MI is different than within about three
4 days of the MI?

5 MR. LAURENCE: Objection; form.

6 THE WITNESS: My opinion here is
7 unchanged. This is about stability.

8 BY MR. WILKERSON:

9 Q And in both instances of initiating
10 within about three days and initiating within
11 about five days, the patient can be stable before
12 or around day two. Right?

13 A Again, pretty common practice to
14 discharge patients home on day two to three.
15 They're clearly stable. I would be in big trouble
16 if I sent someone home unstable. And, obviously,
17 three days is less than five.

18 Q But within five days includes the day
19 two stable patient, the day three stable patient.
20 Right?

21 MR. LAURENCE: Objection; form.

22 THE WITNESS: Matt, once again, I'm

1 perhaps not understanding where you're trying to
2 go. I think I've been pretty clear that when a
3 patient is stable, they can go home.

4 BY MR. WILKERSON:

5 Q I -- I get that part. I'm trying to
6 understand a little bit why it's your opinion that
7 there's no overlap between within about three days
8 of the MI and the phrase "within five days of the
9 MI."

10 A Perhaps because I don't understand why
11 you're asking.

12 Q Well, I'm asking because it -- in your
13 declaration, it's your opinion that the -- the
14 provisional application doesn't teach this within
15 three days. Right? And I'm trying to understand
16 from your perspective why a POSA would read within
17 five days to not overlap with within about three
18 days.

19 A I'm struggling here, Matt. Because I
20 don't think we have a math problem. I think we
21 have a legal problem, and I don't understand the
22 question.

1 Q Okay. We can -- we can try to simplify,
 2 I suppose. And -- and perhaps your answer of we
 3 don't have a math dispute revolves it.

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

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

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

Ex. 2071 at 86:1–92:20.

B. Quotes Related to Ground 2 and 3

32. I am very familiar with all aspects of the COLCOT study including the original publication regarding the COLCOT study that was published by Dr. Tardif in 2019, as well as its brief summary from clinicaltrials.gov, which is referred to as the COLCOT Protocol and is Exhibit 1006. The Patent Owner makes statements

about my deposition testimony regarding the brief summary from clinicaltrials.gov that are incorrect.

33. First, the Patent Owner overstates that I testified to not recalling reviewing Exhibit 1006.

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.

Paper 21 at 2 (Introduction section).

34. The section of my deposition testimony cited in the Response is reproduced below.

8 Q Okay. And now we're looking at the
9 COLCOT protocol that you relied on. And for
10 anticipation, you rely on one reference. Do you
11 understand that?

12 A Let me — let me go back to where we
13 were several hours ago. I've been in this field
14 for 30, 35 years. When I say rely on the
15 protocol, it could be from reading the actual
16 protocol, it could be some of my own clinical
17 trials, from writing the actual protocol,
18 sometimes we work on clinical — I mean,
19 "protocol" means a lot of — I mean, it's — you
20 know, it's — the protocol is how will this
21 clinical trial be conducted. What's on the
22 clintrials.gov website is usually a very brief
1 summary of that.

Ex. 2071 at 136:8–137:1.

35. The Patent Owner made a similar statement elsewhere in the Response with additional citations:

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.

Paper 21 at 21.

36. Below are the deposition transcript pages correlating to the additional citations.

1 you know, I don't – I don't understand what
2 you're asking me.

3 Q I – I – I'm trying to understand
4 because I want to make sure we're on the same
5 page that when we were looking just a minute ago
6 at Exhibit 7, which from your definition is
7 Exhibit 1006 that that's the same reference that
8 you had your opinions that these claims are
9 anticipated by.

10 A And what I'm trying to say, Matt, is
11 that in my recollection of thinking through all
12 the complexities of this issue and all the various
13 things that go into a scientific idea and a
14 scientific concept over time, and as someone who's
15 lived in this field intimately for at least
16 30 years, I can't tell you explicitly which one of
17 these. But I can tell you that it says an updated
18 version of what you're asking me about.

19 So I'm assuming it was an updated
20 version, which is probably the actual trial
21 protocol, not this brief summary. But I can't –
22 I mean, that's, you know, I've asked – you've

1 asked me that several times now.

2 Q So is it your opinion that you're --
3 you're unsure of which reference you relied upon
4 to -- to conclude that Claims 27, 29 through 36
5 and 39 are anticipated?

6 A Do you know, Matt --

7 MR. LAURENCE: Objection; form.

8 THE WITNESS: I couldn't even tell you
9 what those claims are right now. If you want to
10 go through them slowly, we can. But my point is,
11 it says an updated version. To me, in plain
12 English, that suggests it's probably the actual
13 protocol, not this brief summary. But I don't
14 know what else to tell you.

15 BY MR. WILKERSON:

16 Q Okay. If you want, let's go to the --
17 to the Appendix B at page 315 through 318. And if
18 you can --

19 A I'm sorry. Appendix -- Appendix B of
20 what document?

21 Q Of your declaration.

22 A Okay. And can you give me the

1 page number again?

2 Q Yeah. 315.

3 A All right. Thank you. Just a sec.

4 Q Yeah, no problem.

5 A I'm doing my best to keep this thing
6 from hitting the floor.

7 Okay. I'm on 315.

8 Q Okay. And then 315 goes through 318 for
9 Appendix B.

10 A Yes.

11 Q Do you have cited anywhere in there what
12 you're referring to as the actual protocol?

13 A Going through this briefly, I don't see
14 anything referring to any protocol in this
15 particular appendix.

Ex. 2071 at 139:1–141:15.

37. Reviewing these sections of my deposition transcript makes it clear that at no point do I ever say that I did not recall seeing COLCOT, nor that I would not rely upon a clinicaltrials.gov protocol.

38. I clearly state that the clinicaltrials.gov reference is a brief summary of the clinical trial protocol. In my own scientific work, I would generally refer to the actual long-form trial protocol, the one provided to investigators and regulators. However, for the purposes of my first declaration I reviewed the clintrials.gov protocol. It was not necessary to refer to the long-form trial protocol for the purpose of my first declaration because the clinicaltrials.gov reference includes all relevant details of

the treatment method used in the clinical trial, including a description of the background, the purpose, the dose, dosage regime, patient inclusion and exclusion criteria, outcomes, control group, and duration of the trial. This is a requirement of registration of a clinical trial.

39. The full-length clinical trial protocol of the COLCOT trial runs to 217 pages and it is fair to refer to the six-page [clintrials.gov](https://clinicaltrials.gov) reference as “brief” or even “very brief” in comparison. Because it includes all relevant details, and for reasons of brevity, I refer to the [clintrials.gov](https://clinicaltrials.gov) summary in my first declaration as a “protocol.”

40. The statements by the Patent Owner to the effect that I testified that I did not see, or would not rely upon, Exhibit 1006, entirely mischaracterize what I said and also the facts of the matter.

41. Second, the Patent Owner attempts to mislead by stating I testified I would not rely on the brief summary from clinicaltrials.gov.

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.

Paper 21 at 21. The Patent Owner repeated the incorrect assertion in its Introduction section as quoted above. *Id.* at 2. While I would rely on the complete protocol for

scientific purposes, the brief summary suffices for analyzing patentability because the brief summary includes the pertinent information

42. Below are the deposition transcript pages cited above that have not yet been previously reproduced herein.

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1 my deposition what did I specifically rely on, and
2 it says updated version. If you want to show me
3 an updated version, I can describe --

4 Q Is --

5 A -- whether that looks like what I saw or
6 not. I don't know. I mean.

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

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

16 But I mean, the full protocol is
17 usually -- I mean, sometimes they go on to 150,
18 200, 300, you know, pages. This is -- this is --
19 this is, by definition, meant to be a website that
20 people go to to, you know, do a quick search, what
21 are -- what are people studying out there? And
22 it's a website -- it's a very important website so

1 that, you know, pharmaceutical companies can't
 2 hide what they're doing. So it's – it's a public
 3 disclosure website, right? That's what its
 4 purpose is. But it's not meant to be definitive
 5 protocol.

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

Ex. 2071 at 146:11–147:11.

43. The Patent Owner made a similar assertion a third time with citations to additional sections of my deposition transcript:

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.

Paper 21 at 21.

44. Below is the section of transcript of my deposition cited by the Patent Owner in the above excerpt.

1 Q And then there's a document label, and
2 it says a date of the document. Do you see where
3 it says 2018 November 15th?

4 A I see that.

5 Q And then right below that, it says
6 "uploaded 2020 July 16th"?

7 A I see that.

8 Q Okay.

9 MR. WILKERSON: So now we can turn to
10 Tab 6. And we'll mark this as Ridker Exhibit 9.

11 (RIDKER Exhibit 9 was marked for
12 identification and is attached to the transcript.)

13 THE WITNESS: I'm sorry, Matt. Just
14 because I don't have a lot of table space, are we
15 done with this?

16 BY MR. WILKERSON:

17 Q Yeah, you can put that -- you can put
18 that away.

19 A Okay.

20 Q Okay. And do you have the Exhibit 9 in
21 front of you?

22 A Yes.

1 Q Okay. Do you recognize this document?

2 A **This looks more familiar to me than the**
3 **other ones do, yes. I –**

4 Q Okay. And do you see in the upper
5 left-hand corner, there's a date, November 15th,
6 2018?

7 A **Yes.**

8 Q Okay. And this looks familiar to you.
9 Did you review it in forming your opinions for
10 this case?

11 A **In forming my opinions in this case, I**
12 **did review at various times the main paper of**
13 **COLCOT. I did review its protocol. Whether it's**
14 **this exact one or not, my guess is the one I would**
15 **have reviewed probably would have been the one**
16 **that one can download in the public space from the**
17 **New England Journal.**

18 **But I mean, it's probably quite similar,**
19 **if not the same. I can't – I'd have to actually**
20 **read the thing and cross tab it to make sure. But**
21 **at least it looks a lot closer than the other ones**
22 **you've showed me. Let's put it that way.**

Ex. 2071 at 151:9–152:22.

45. The Patent Owner concluded:

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.

Paper 21 at 21.

46. Reviewing this section of my deposition transcript makes it clear that I never made the characterizations of the COLCOT Protocol asserted by the Patent Owner. In addition to distorting the record regarding my deposition testimony, the Patent Owner also ignores my testimony in my first declaration regarding the COLCOT Protocol. Ex. 1049 at ¶¶ 30-33, 37, 54-56, 76-79.

III. LOADING DOSE

47. As I noted in my first declaration, “A skilled cardiologist would understand that Bouabdallaoui’s disclosure of administering 0.5 mg colchicine once daily is a complete dosing protocol that does not involve a higher preloading dose.” EX1049 ¶ 62. I made that statement even though Bouabdallaoui and Nidorf do not explicitly say that no loading dose was given.

48. I understand that the Patent Owner disagrees with this opinion of mine. *See* Paper 21 at 36. I understand that the Patent Owner argues that silence regarding a loading dose of colchicine implies that a loading dose should be administered because that is, in the Patent Owner’s view, part of the “standard therapies” for colchicine. *Id.*

49. I disagree. A POSA would understand that a loading dose of the active ingredient being studied in a clinical trial such as the ones reported in Nidorf and Bouabdallaoui would be expressly stated if it were to be administered, and that the absence of any mention of a loading dose of the active ingredient being studied means that no loading dose should be administered. Because dosing errors are so commonly made and can be so dangerous, physicians are trained to be explicit when they talk about dose requirements to their patients as well as in all written documents, including clinical trial protocols and results. Had the authors wanted a loading dose to be given, they would have absolutely stated so.

IV. CERTIFICATION

50. In signing this declaration, I recognize that this declaration will be filed in support of the Petitioner in case number IPR2023-01064 at the U.S. Patent and Trademark Office.

51. I reserve the right to supplement my opinions in the future to respond to any arguments that the Patent Owner raises and to take into account new information as it becomes available to me.

52. I acknowledge that, as part of this IPR, I may be subject to cross-examination in the United States regarding the content of this declaration. If cross-examination is required of me, I will make myself reasonably available for cross-examination within the United States during the time allotted for cross-examination.

53. I declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true and, further, that these statements were made with the knowledge that willful false statements and the like are punishable by fine, imprisonment, or both, under Section 1001 of Title 18 of the United States Code.

Executed on July 11, 2024.



Paul Ridker, M.D.