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Paper 13
Date: August 14, 2025

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

CSPC PHARMACEUTICAL GROUP LIMITED,
CSPC OUYI PHARMACEUTICAL CO., LTD., AND
CONJUPRO BIOTHERAPEUTICS, INC.,
Petitioner,

v.

IPSEN BIOPHARM LTD.,
Patent Owner.

IPR2025-00505
Patent 11,344,552 B2

Before JEFFREY N. FREDMAN, ZHENYU YANG, and TIMOTHY G. MAJORS, *Administrative Patent Judges.*

FREDMAN, *Administrative Patent Judge*.

DECISION
Granting Institution of *Inter Partes* Review
35 U.S.C. § 314

I. INTRODUCTION

CSPC Pharmaceutical Group Limited, CSPC Ouyi Pharmaceutical Co., Ltd., and Conjupro Biotherapeutics, Inc. ("Petitioner") filed a Petition (Paper 1, "Pet.") requesting *inter partes* review of claims 1–15 (the "challenged claims") of U.S. Patent No. 11,344,552 B2 (Ex. 1001, "the '552 patent"). Ipsen Biopharm Ltd. ("Patent Owner") filed a Preliminary Response. Paper 9 ("Prelim. Resp.").[1]

We have authority under 35 U.S.C. § 6 and 35 U.S.C. § 314, which provides that an *inter partes* review may not be instituted unless the information presented in the Petition "shows that there is a reasonable likelihood that the petitioner would prevail with respect to at least 1 of the claims challenged in the petition."

A decision to institute under § 314 may not institute on fewer than all claims challenged in the petition. *SAS Inst., Inc. v. Iancu*, 138 S. Ct. 1348, 1359–60 (2018). In addition, if the Board institutes trial, it will "institute on all grounds in the petition." PTAB Consolidated Trial Practice Guide ("CTPG"), 5–6 (Nov. 2019); *see also PGS Geophysical AS v. Iancu*, 891 F.3d 1354, 1360 (Fed. Cir. 2018) (interpreting the statute to require "a simple yes-or-no institution choice respecting a petition, embracing all challenges included in the petition").

Having considered the arguments and evidence presented in the Petition and the Preliminary Response, for the reasons described below, we institute *inter partes* review.

[1] The parties also filed briefs directed to discretionary denial issues. *See* Papers 8, 10. The Acting Director ruled on discretionary denial issues. *See* Paper 11. We do not further address discretionary denial issues here.

This decision to institute trial is not a final decision as to patentability of claims for which inter partes review is instituted. Our final decision will be based on the full record developed during trial.

II. REAL PARTIES-IN-INTEREST

Petitioner identifies CSPC Pharmaceutical Group Limited, CSPC Ouyi Pharmaceutical Co., Ltd., and Conjupro Biotherapeutics, Inc. as the real parties-in-interest. Pet. 4. Patent Owner states "Ipsen Biopharm LTD. is the Patent Owner and the Real Party-in-Interest in this proceeding. Ipsen Biopharmaceuticals, Inc. and Ipsen Pharma SAS are also Real Parties-in-Interest." Paper 4, 2.

Patent Owner asserts the "petition fails to identify all real parties-in-interest, because it fails to identify Cipla USA, Inc. ('Cipla')." Prelim. Resp. 16.

We disagree with Patent Owner's arguments. On this record, and as explained below, we are not currently persuaded that Cipla is an unnamed RPI of Petitioner. As a result, we do not deny institution due to these alleged real parties-in-interest or privies.

A. Summary of Applicable Law

A petitioner must "identif[y] all real parties in interest" in an *inter partes* review petition (37 C.F.R. § 312(a)(2)), and the petition must be filed no more than one year after "the date on which the petitioner, real party in interest, or privy of the petitioner is served with a complaint alleging infringement of the patent" (35 U.S.C. § 315(b)).

A petitioner's identification of RPIs "should be accepted unless and until" a patent owner "produce[s] some evidence that tends to show that a particular third party should be named a real party in interest." *Worlds Inc. v.*

Bungie, Inc., 903 F.3d 1237, 1243–44 (Fed. Cir. 2018). "A mere assertion that a third party is an unnamed real party in interest, without any support for that assertion, is insufficient to put the issue into dispute." *Id*. Once the patent owner has sufficiently raised the issue, the "petitioner bears the burden of persuasion to demonstrate that its petitions are not time-barred under § 315(b) based on a complaint served on a real party in interest more than a year earlier." *Id*. at 1242.

Determining whether a non-party is a "real party in interest" or "privy" is a highly fact-dependent inquiry that takes into consideration how courts have viewed these terms. CTPG 13 (citing *Taylor v. Sturgell*, 553 U.S. 880, 895 (2008); Charles Alan Wright, Arthur R. Miller & Edward H. Cooper, Federal Practice & Procedure §§ 4449, 4451). This inquiry demands a flexible approach that takes into account both equitable and practical considerations, with an eye toward determining whether the non-party is a clear beneficiary that has a preexisting, established relationship with the petitioner. *Applications in Internet Time, LLC v. RPX Corp*., 897 F.3d 1336, 1351 (Fed. Cir. 2018) ("AIT").

B. Cipla USA, Inc. ("Cipla")

According to Patent Owner, Cipla is an RPI, but was not properly named. Prelim. Resp. 16. Patent Owner asserts Cipla has "an interest in the commercialization of the Proposed Conjupro Product by virtue of an exclusive license agreement with CSPC. *See* Ex. 2021 (CSPC Press Release). This relationship renders Cipla a real party-in-interest for purposes of CSPC's petition. CSPC's failure to identify Cipla as such runs afoul of statutory requirements." *Id.*

However, Patent Owner has not shown that circumstances exist that would require dismissal of the proceeding as barred under § 315(b) if the unnamed party were added as a real party in interest. Patent Owner has also not alleged any discovery abuse at this time.

We determine that we need not address whether Cipla is an unnamed RPI at this stage. The parties may further address this issue during the trial portion of the proceedings. As the Board explained in *SharkNinja*, it "better serves the interest of cost and efficiency" when the Board does not engage in the "extensive analysis" required to determine whether a party is an unnamed RPI if the result of that analysis has no material impact on the proceeding. *SharkNinja v. iRobot Corp*., IPR2020-00734, Paper 11 at 19–20 (PTAB Oct. 6, 2020) (precedential). Here, it is undisputed that Petitioner could have named Cipla as an RPI in its Petition without triggering a statutory bar or estoppel under 35 U.S.C. § 315.

III. RELATED MATTERS

Both Petitioner and Patent Owner state that they are unaware of any judicial or administrative proceedings that would either affect or be affected by a decision regarding this Petition. *See* Pet. 4; Paper 4, 2.

IV. THE '552 PATENT

The '552 patent states the "disclosure relates to novel therapies useful in the treatment of pancreatic cancer, including the use of liposomal irinotecan in combination with 5-fluorouracil and oxaliplatin for the (first line) treatment of patients diagnosed with previously untreated pancreatic cancer." Ex. 1001, 1:21–25. The '552 patent teaches

> The invention is based in part on several pre-clinical discoveries. First, liposomal irinotecan improved anti-tumor activity of

> the topoisomerase 1 inhibitor SN-38 (an active metabolite of irinotecan) relative to exposure-matched doses of non-liposomal irinotecan. Second, liposomal irinotecan combined with 5-fluorouracil and oxaliplatin consistently improved tumor growth inhibition and survival in mouse xenograft models of pancreatic cancer relative to non-liposomal irinotecan, without exacerbating the baseline toxicities of these agents. In addition, the invention is based in part on the discovery that the administration of a dose of mg/m^2 liposomal irinotecan was not well tolerated in humans when administered in combination with 60 mg/m^2 oxaliplatin, 2400 mg/m^2 5-fluorouracil and 400 mg/m^2 (l+d) leucovorin.

Id. at 2:47–61.

V. ILLUSTRATIVE CLAIMS

Petitioner challenges claims 1–15, of which claims 1 and 12 are independent and are reproduced below:

> 1. A method of treating metastatic adenocarcinoma of the pancreas in a human patient who has not previously received an antineoplastic agent to treat the metastatic adenocarcinoma of the pancreas, the method comprising administering an antineoplastic therapy to the patient once every two weeks, the antineoplastic therapy consisting of:
>
> a. 60 mg/m^2 of liposomal irinotecan,
>
> b. 60 mg/m^2 oxaliplatin,
>
> c. 200 mg/m^2 of the (1)-form of leucovorin or 400 mg/m^2 of the (l+d) racemic form of leucovorin, and
>
> d. 2,400 mg/m^2 5-fluorouracil;
>
> to treat the metastatic adenocarcinoma of the pancreas in the human patient.

> 12. A method of treating metastatic adenocarcinoma of the pancreas in a human patient who has not previously received gemcitabine to treat the metastatic adenocarcinoma of the pancreas, the method comprising administering an antineoplastic therapy to the patient once every two weeks, the antineoplastic therapy consisting of:
>
> a. 60 mg/m^2 of liposomal irinotecan,

b. 60 mg/m^2 oxaliplatin,
c. 200 mg/m^2 of the (1)-form of leucovorin or 400 mg/m^2 of the (l+d) racemic form of leucovorin, and
d. 2,400 mg/m^2 5-fluorouracil;
to treat the metastatic adenocarcinoma of the pancreas in the human patient.

Ex. 1001, 46:64–47:9; 48:7–19.

VI. ASSERTED GROUNDS

Petitioner contends that the challenged claims are unpatentable based on the following grounds. Pet. 6.

Reference	Basis	Claims Challenged
Conroy,[2] Conroy Protocol,[3] Conroy Appendix,[4] Mahaseth,[5] Bayever,[6] Saif,[7]	§ 103	1, 3–6, 8–14

[2] Conroy, et al., *FOLFIRINOX versus Gemcitabine for Metastatic Pancreatic Cancer*, 364(19) N. Engl. J. Med. 1817–25 (2011) (Ex. 1003, "Conroy").

[3] Certified English Translation of the Protocol of Conroy, et al, https://www.nejm.org/doi/full/10.1056/NEJMoa1011923#APPNEJMoa1011923PRO (2011) (Ex. 1004, "Conroy Protocol").

[4] Conroy Supplementary Appendix, 364(19) N. Engl. J. Med. 1–17 Supplementary Appendix (2011) (Ex. 1017, "Conroy Appendix").

[5] Mahaseth et al., *Modified FOLFIRINOX Regimen With Improved Safety and Maintained Efficacy in Pancreatic Adenocarcinoma*, 42(8) Pancreas 1311–15 (2013) (Ex. 1005, "Mahaseth").

[6] Bayever et al., WO 2013/188586 A1, published Dec. 19, 2013 (Ex. 1006, "Bayever").

[7] Saif, *MM-398 Achieves Primary Endpoint of Overall Survival in Phase III Study in Patients with Gemcitabine Refractory Metastatic Pancreatic Cancer*, 15(3) J. Pancreas 278–79 (2014) (Ex. 1007, "Saif").

Ko,[8] Cantore[9]		
Conroy, Conroy Protocol, Conroy Appendix, Mahaseth, Bayever, Saif, Ko, Cantore, Masi,[10] Ginocchi[11]	§ 103	2, 7, 15
Conroy, Conroy Protocol, Conroy Appendix, Mahaseth, Bayever, Saif, Ko, Cantore, Masi, Ginocchi, Carnevale,[12] Dean[13]	§ 103	1–15

Petitioner relies also on the Declaration of Mark J. Ratain, M.D. *See* Ex. 1002.

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[8] Ko, et al., *A multinational phase 2 study of nanoliposomal irinotecan sucrosofate (PEP02, MM-398) for patients with gemcitabine-refractory metastatic pancreatic cancer*, 109(4) Br. J. of Cancer 920–25 (2013) (Ex. 1008, "Ko").

[9] Cantore, et al., *Combined Irinotecan and Oxaliplatin in Patients with Advanced Pre-Treated Pancreatic Cancer*, Oncology, 67(2) Oncology 93–97 (2004) (Ex. 1009, "Cantore").

[10] Masi, et al., *First-line treatment of metastatic colorectal cancer with irinotecan, oxaliplatin and 5-fluorouracil/leucovorin (FOLFOXIRI): results of a phase II study with a simplified biweekly schedule*, 15 Annals of Oncology 1766–72 (2004) (Ex. 1012, "Masi").

[11] Ginocci, et al., *MODIFIED FOLFOXIRI IN ADVANCED PANCREATIC CANCER*, 23(9 Suppl) Annals of Oncology ix238 (2012) (Ex. 1016, "Ginocci").

[12] Carnevale and Ko, *MM-398 (nanoliposomal irinotecan):emergence of a novel therapy for the treatment of advanced pancreatic cancer*, 12(4) Future Oncology 453–464 (2016) (Ex. 1013, "Carnevale").

[13] Dean, et al., *A randomized, open-label phase II study of nanoliposomal irinotecan (nal-IRI)containing regimens versus nab-paclitaxel plus gemcitabine in patients with previously untreated metastatic pancreatic adenocarcinoma (mPAC)*, 34(4 Suppl.) J Clin Oncol. tps482 1–5 (2016) (Ex. 1014, "Dean").

VII. LEVEL OF ORDINARY SKILL IN THE ART

Petitioner contends that a

> person of ordinary skill in the art (POSA) would have been an M.D. and/or Pharm. D who would have completed training in medical oncology, particularly in the field of gastrointestinal (GI) cancers, or a Ph.D. in clinical pharmacology, pharmaceutical sciences, pharmaceutics, and/or drug delivery, also particularly in the field of GI cancers, or their equivalents, along with at least 1-2 years of post-doctoral experience.

Pet. 26 (citing Ex. 1002 ¶¶ 44–46).

Patent Owner states it disagrees with Petitioner's "definition of a POSA but assumes their definition for purposes of the arguments presented herein." Prelim. Resp. 6.

At this stage in the proceeding, we find that Petitioner's analysis reasonably establishes a level of ordinary skill in the art as it directly relates to those deciding treatments based on the prior art references. The level of ordinary skill in the art usually is evidenced by the prior art references themselves. *See, e.g.*, Ex. 1003, 1817, author list. *See Okajima v. Bourdeau*, 261 F.3d 1350, 1355 (Fed. Cir. 2001); *In re GPAC Inc.*, 57 F.3d 1573, 1579 (Fed. Cir. 1995).

VIII. CLAIM INTERPRETATION

In an *inter-partes* review, we interpret a claim "using the same claim construction standard that would be used to construe the claim in a civil action under 35 U.S.C. 282(b)." 37 C.F.R. § 42.100(b). Under this standard, we construe the claim "in accordance with the ordinary and customary meaning of such claim as understood by one of ordinary skill in the art and the prosecution history pertaining to the patent." *Id.*

A. Petitioner's Position

1. *"Treating" and "Treatment"*

Petitioner asserts that the terms "treating" and "treat," as used in the '552 claims, should be interpreted as "attempting to cause a therapeutic improvement but not requiring actual efficacy." Pet. 27. Petitioner cites Dr. Ratain's testimony that:

> Treating a patient is always with the attempt or intent to cause a therapeutic improvement of the patient, which, in the case of metastatic pancreatic cancer, could be reduced tumor growth or increased overall survival in the patient. However, "treatment" does not require a certain level of efficacy, and oftentimes, treating patients with this disease does not result in therapeutic improvement.

Ex. 1002 ¶ 50.

Petitioner also asserts "nothing in the claim language . . . requires that 'treating' brings about a particular result, such as clinical efficacy." Pet. 27 (citing Ex. 1002 ¶ 51). Petitioner notes that the '552 patent summary describes "a number of different dosing options of this general method, defined solely by administration of the drugs and not by clinical efficacy." *Id.* at 28 (citing Ex. 1001, 2:29–46; Ex. 1002 ¶¶ 52–56).

Petitioner notes that the '552 patent does have an embodiment reciting a "***therapeutically effective amount***," and points to US Provisional 60/208,209 from which the '552 claims priority as stating "[a]s used herein, 'effective treatment' refers to treatment producing a beneficial effect, e.g., amelioration of at least one symptom of a disease or disorder." Pet. 28 (citing Ex. 1001, 18:34–38; Ex. 1015 ¶ 36). Petitioner then asserts that "it is clear that the patentees knew how to use the term 'therapeutically effective' . . . ***but deliberately chose to delete*** 'therapeutically effective' and 'effective

treatment' from the claim language, which compels against injecting a therapeutic result into the Challenged Claims." Pet. 28–29 (citing Ex. 1015 ¶¶ 36, 74–76).

Lastly, Petitioner asserts that their "construction is consistent with a long line of decisions where the plain and ordinary meaning of 'treating' in method of treating claims does not require any therapeutic improvement in terms of clinical efficacy but covers any attempt or purpose to provide therapeutic improvement." Pet. 29.

B. Patent Owner's Position

1. *"Treating" and "Treatment"*

Patent Owner asserts that "'[t]reatment,' as used in the '552 patent, refers to management and/or care comprising antineoplastic therapy in accordance with the claims and specification." Prelim. Resp. 8. Patent Owner asserts "the claims cover effective methods of treatment. And [Petitioner]'s proposed construction, which does not require actual efficacy, is at odds with the plain and ordinary meaning of 'treat' and 'treatment.'" *Id.*

Patent Owner asserts that for Grounds 1 and 2, Petitioner "argues that 'treating' and 'treat' should be understood to mean 'attempting to cause a therapeutic improvement but not requiring actual efficacy'" and that based on "this construction, [Petitioner] argues that the '552 patent's effective filing date is August 21, 2015." *Id.* at 8–9 (citing Pet. 26–30, 36). Patent Owner asserts Petitioner's "proposed construction finds no support anywhere in the '552 patent specification." *Id.* at 9. Patent Owner instead asserts that "the '552 patent specification teaches that the claimed doses are 'effective.'" *Id.* at 9–10 (citing Ex. 1001, 9:57–10:54, 18:32–41, 12:6–11, 12:35–45, 12:53–58).

Patent Owner asserts Petitioner "cites cases decided on different factual circumstances from those present here" and "is incorrect to suggest that the intrinsic record here is analogous to that of the cases it cites." *Id.* at 11. Patent Owner asserts Petitioner "identifies no credible extrinsic evidence in support of its proposed construction. [Petitioner] cites no technical dictionary definitions. To the extent that [Petitioner] relies on its expert Dr. Ratain, his testimony is either duplicative of [Petitioner]'s arguments or uninformed by the intrinsic record." *Id.*

Patent Owner asserts that for Ground 3, Petitioner "relies on an alternative, unspecified construction of 'treat' and 'treating' that would require 'a showing of clinical efficacy.'" *Id.* at 12. Patent Owner asserts Petitioner "cites no support in the specification for its alternative 'construction.' At most, [Petitioner] suggests that the '552 patent applicant's arguments during prosecution compel a claim requirement of clinical efficacy." *Id.*

C. Analysis

1. *"Treating" and "Treatment"*

We first turn to the Specification which is, "[i]n most cases, the best source for discerning the proper context of claim terms." *Metabolite Labs., Inc. v. Lab. Corp. of Am. Holdings*, 370 F.3d 1354, 1360 (Fed. Cir. 2004). The '552 patent teaches a "method of treating pancreatic cancer can comprise the administration of an antineoplastic therapy of liposomal irinotecan, oxaliplatin, and 5-fluorouracil once every two weeks to the patient." Ex. 1001, 2:26–30. The '552 patent teaches, in a mouse tumor model, that treatment with the "addition of oxaliplatin to MM-398+5-FU further improves response by significantly delaying tumor progression as

compared to MM-398 monotherapy." *Id.* at 8:10–12. The '552 patent teaches that during the proposed Phase II/III study,

> [i]f the time required for recovery from toxicity is more than 3 weeks, the patient should be discontinued from the study, unless the patient is benefiting from the study treatment, in which case the patient's continuation on study should be discussed between Investigator and Sponsor or its designee regarding risks and benefits of continuation.

Id. at 33:4–9. The '552 patent further states "[f]or each patient, progression free survival time is determined as the time from randomization . . . to the first documented radiographical Progression of Disease (PD) . . . or death from any cause, whichever comes first." *Id.* at 40:58–63.

Thus, the '552 patent teaches that patients may or may not receive some therapeutic benefit from the treatment and also recognizes that any therapeutic benefit may result in prolonging life, but not necessarily result in complete remission of the pancreatic tumor.

This understanding is consistent with Dr. Ratain's testimony that "[t]reating a patient is always with the attempt or intent to cause a therapeutic improvement of the patient, which, in the case of metastatic pancreatic cancer, could be reduced tumor growth or increased overall survival in the patient." Ex. 1002 ¶ 50. We are unpersuaded, however, by Dr. Ratain's statement equating "***treatment with a saline control***" with the claimed "treating metastatic adenocarcinoma," because the claim is addressing a disease condition whereas the example in Figure 6A is clearly providing a control, without any expectation of therapeutic benefit. *See id*. ¶ 55.

We are not persuaded, on this record, that because Patent Owner did not include the phrase "therapeutically effective amount" in the claims, the

claims solely relate to "administering" the antineoplastic therapies without any resulting therapeutic benefit. Rather, on this record, we agree with Patent Owner that the ordinary understanding of a claim reciting a "method of treating metastatic adenocarcinoma of the pancreas" that comprises "administering an antineoplastic therapy to the patient" in order "to treat the metastatic adenocarcinoma of the pancreas" is that the "treatment" would have more than a *de minimis* therapeutic benefit or efficacy for the patient being treated.

To the extent that Patent Owner's position would require some particular degree of clinical efficacy, however, we do not find that position supported by the evidence. We need not address the exact degree of benefit or efficacy obtained, as the level of clinical efficacy is not a claim limitation. *See, e.g.*, *Wellman, Inc. v. Eastman Chem. Co.*, 642 F.3d 1355, 1361 (Fed. Cir. 2011) ("[C]laim terms need only be construed 'to the extent necessary to resolve the controversy.'") (quoting *Vivid Techs., Inc. v. Am. Sci. & Eng'g, Inc*., 200 F.3d 795, 803 (Fed. Cir. 1999)).

IX. PRINCIPLES OF LAW

"In an [*inter partes* review], the petitioner has the burden from the onset to show with particularity why the patent it challenges is unpatentable." *Harmonic Inc. v. Avid Tech., Inc*., 815 F.3d 1356, 1363 (Fed. Cir. 2016) (citing 35 U.S.C. § 312(a)(3) (requiring *inter partes* review petitions to identify "with particularity . . . the evidence that supports the grounds for the challenge to each claim")). This burden of persuasion never shifts to the patent owner. *See Dynamic Drinkware, LLC v. Nat'l Graphics, Inc*., 800 F.3d 1375, 1378 (Fed. Cir. 2015) (discussing the burden of proof in *inter partes* review).

The question of obviousness is resolved on the basis of underlying factual determinations including: (1) the scope and content of the prior art; (2) any differences between the claimed subject matter and the prior art; (3) the level of ordinary skill in the art; and (4) objective evidence of nonobviousness. *Graham*, 383 U.S. at 17–18.

The obviousness inquiry also typically requires an analysis of "whether there was an apparent reason to combine the known elements in the fashion claimed by the patent at issue." *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007) (citing *In re Kahn*, 441 F.3d 977, 988 (Fed. Cir. 2006) (requiring "articulated reasoning with some rational underpinning to support the legal conclusion of obviousness")). A petitioner cannot prove obviousness with "mere conclusory statements." *In re Magnum Oil Tools Int'l, Ltd.*, 829 F.3d 1364, 1380 (Fed. Cir. 2016). Rather, a petitioner must articulate a sufficient reason why a person of ordinary skill in the art would have combined the prior art references. *In re NuVasive, Inc.*, 842 F.3d 1376, 1382 (Fed. Cir. 2016).

We analyze the asserted ground of unpatentability in accordance with the above-stated principles.

X. ANALYSIS

A. Overview of Prior Art cited for Obviousness

1. *Conroy (Ex. 1003)*

Conroy is a scientific paper published in 2011 reporting on a phase 2-3 clinical trial "of a combination chemotherapy regimen consisting of oxaliplatin, irinotecan, fluorouracil, and leucovorin (FOLFIRINOX) as compared with gemcitabine as first-line therapy in patients with metastatic pancreatic cancer." Ex. 1003, 1817. Conroy treated a patient population with

"measurable metastatic pancreatic adenocarcinoma that had not previously been treated with chemotherapy." *Id*. at 1818. Conroy teaches that

> FOLFIRINOX consisted of oxaliplatin at a dose of 85 mg per square meter, given as a 2-hour intravenous infusion, immediately followed by leucovorin at a dose of 400 mg per square meter, given as a 2-hour intravenous infusion, with the addition, after 30 minutes, of irinotecan at a dose of 180 mg per square meter, given as a 90-minute intravenous infusion through a Y-connector. This treatment was immediately followed by fluorouracil at a dose of 400 mg per square meter, administered by intravenous bolus, followed by a continuous intravenous infusion of 2400 mg per square meter over a 46-hour period every 2 weeks.

Id. at 1819. Conroy teaches that "protocol-specified treatment modifications were permitted (see the Supplementary Appendix[])]" and that the "median relative dose intensities of fluorouracil, irinotecan, oxaliplatin, and gemcitabine were 82%, 81%, 78%, and 100%, respectively." *Id*. at 1819, 1820.

Conroy teaches "FOLFIRINOX was an effective first-line treatment option for patients with metastatic pancreatic adenocarcinoma and good ECOG performance status. The median overall survival was significantly prolonged, with an increase of 4.3 months in the FOLFIRINOX group as compared with the gemcitabine group." *Id*. at 1822.

2. *Conroy Protocol (Ex. 1004)*

The Conroy Protocol is supplemental material that was published with the Conroy paper in 2011. Ex. 1003, 1819; 1004, 1. The Conroy protocol shows a table depicting dose changes in the Folfirinox regimen due to hematological toxicity, reproduced below:

TREATMENT A: Folfirinox

CBC at D15	CYCLE DELAY	DOSE REDUCTION		
		Irinotecan (CPT-11)	Oxaliplatin (L-OHP)	LV5FU
PNN ≥1.5 x 10^9/L and platelets ≥75 x 10^9/L	No cycle delay	No dose reduction		
PNN <1.5 x 10^9/L	Delay treatment until PNN 1,500 (until D22 or D29 if necessary). If no recovery at D29, **discontinuation of treatment***	1st episode: dose reduction to 150 mg/m² 2nd episode: dose maintained at 150 mg/m² 3rd episode: **discontinuation of treatment**	1st episode: no dose reduction 2nd episode: reduce dose to 60 mg/m² 3rd episode: **discontinuation of treatment**	1st episode: eliminate bolus on D1
Platelets <75 x 10^9/L	Delay treatment until recovery (platelets ≥75 x 10^9/L) If no recovery at D29, **discontinuation of treatment**	1st episode: no dose reduction 2nd episode: reduce dose to 150 mg/m² 3rd episode: **discontinuation of treatment**	1st episode: reduce dose to 60 mg/m² 2nd episode: maintenance of reduced dose 3rd episode: **discontinuation of treatment**	1st episode: reduce bolus and continuous infusion dose by 25%

* *If there is no recovery after 2 treatment delays, discontinue treatment unless there is a clear clinical benefit: the case will then be discussed with the study coordinator and the sponsor.*

Ex. 1004, 16. This Conroy Protocol table, reproduced above, shows that for patients with certain toxicity events, the protocol has a reduction in Irinotecan dose to 150 mg/m^2, reductions in Oxaliplatin dose to 60 mg/m^2, and eliminates the fluorouracil bolus. *Id.*

3. *Conroy Appendix (Ex. 1017)*

The Conroy Appendix is supplemental material that was published with the Conroy paper in 2011. Ex. 1017, 1; Ex. 1003, 1817. The Conroy Appendix provides similar dose reduction discussions as the Conroy Protocol, and states that "[a]ny other toxicity ≥ grade 2, except anemia and alopecia, can justify a reduction of dose if medically indicated, for example reduction of irinotecan to 150 mg/m² and/or oxaliplatin to 60mg/m² and/or 5FU of 25% depending of the type of adverse event." Ex. 1017, 7.

4. *Mahaseth (Ex. 1005)*

Mahaseth is a scientific paper published in 2013 reporting "a modified FOLFIRINOX regimen in both locally advanced unresectable and metastatic PC [pancreatic cancer] patients with good performance status." Ex. 1005, 1311. Mahaseth teaches the

> modified FOLFIRINOX regimen included oxaliplatin 85 mg/m^2 in water with 5% dextrose intravenously (IV) over 2 hours, leucovorin 400 mg/m^2 in normal saline IV over 90 minutes concurrently with irinotecan 180 mg/m^2 in normal saline IV over 90 minutes, and 5-FU 2400 mg/m^2 in water with 5% dextrose via continuous intravenous infusion over 46 hours. Patients did not receive bolus 5-FU.

Id. at 1312. Mahaseth teaches "[e]ighteen patients required dose reduction. Four patients had only oxaliplatin held due to neuropathy. Five patients had only irinotecan held or reduced due to diarrhea. Nine patients had dose reduction of all agents." *Id*. at 1313. Mahaseth teaches the "modified FOLFIRINOX regimen is well tolerated and has significant activity in metastatic PC. In patients with stage II or III disease, treatment with modified FOLFIRINOX followed by concurrent chemoradiotherapy appears to have promising activity with respect to resectability and survival." *Id.* at 1315.

5. *Bayever (Ex. 1006)*

Bayever is an international patent publication published in 2013 teaching "methods for treating pancreatic cancer in a patient *(i.e.,* a human patient) comprising administering to the patient liposomal irinotecan (e.g., irinotecan sucrose octasulfate salt liposome injection, also referred to as MM-398) alone or in combination with 5-fluorouracil (5-FU) and leucovorin

(together, 5-FU/LV), according to a particular clinical dosage regimen." Ex. 1006, 3. Bayever teaches

> Based upon what is known of the biology of pancreatic cancer, a variety of targeted agents have been evaluated, but only erlotinib, a protein tyrosine kinase inhibitor targeted to EGFR, has been approved for first-line use in advanced pancreatic cancer, and the approval is only for use in combination with gemcitabine. . . . Clinical trials evaluating other targeted agents, including studies testing the antibodies bevacizumab and cetuximab, have been disappointingly negative. Thus, there is an urgent need for improvements in, and effective alternatives to, current therapies for pancreatic cancer.

Id. at 3–4.

Bayever teaches a study design for Arm C including treatment patients with

> MM-398 80 mg/m^2 IV over 90 minutes, every 2 weeks. Patients who are homozygous for UGT1A1*28 allele and are randomized to Arm C, will receive the first cycle of therapy at a reduced dose of 60 mg/m^2. If the patient does not experience any drug related toxicity after the first administration of MM-398, from cycle 2 onwards, the dose may be increased to 80 mg/m2. 5-FU 2400 mg/m^2 IV over 46-hours, every 2 weeks. Levoleucovorin dosed at 200 mg/m^2 or the l + d racemic mixture dosed at 400 mg/m^2 , IV over 30 minutes, every 2 weeks.

Id. at 26–27.

6. *Saif (Ex. 1007)*

Saif is a scientific paper published in 2014 reporting on a phase III study showing that "the combination of MM-398 with 5-fluorouracil (5-FU) and leucovorin achieved an overall survival of 6.1 months, a 1.9 month improvement over the 4.2 month survival demonstrated by the control arm of 5-FU and leucovorin alone." Ex, 1007, 1. Saif teaches: "Now that we have combination of 5-fluorouracil, oxaliplatin, irinotecan, leucovorin

(FOLFIRINOX) as an option for first-line treatment too, how will this regimen fit in the algorithm of the treatment?" *Id*.

7. *Ko (Ex. 1008)*

Ko is a scientific paper published in 2013 reporting a "phase 2 study of PEP02 (liposome encapsulated irinotecan, PharmaEngine Inc, Taipei, Taiwan) in patients with gemcitabine-based chemotherapy failure metastatic pancreatic adenocarcinoma." Ex. 1008, 921. Ko teaches "PEP02 did show clear evidence of antitumour activity in a subset of patients in whom no standard of care therapy otherwise exists." *Id*. at 924. Ko teaches:

> Additional studies may explore this drug's potential role in the first-line setting and as part of combination regimens for APC. Moreover, given the emergence of FOLFIRINOX as a front-line standard in patients with good performance status, the utility of PEP02 in irinotecan-pretreated patients, alone or in combination with gemcitabine, also merits further investigation.

Id. at 924.

8. *Cantore (Ex. 1009)*

Cantore is a scientific paper published in 2004 reporting a phase II study designed "to determine whether combined therapy with oxaliplatin and irinotecan could have utility as a second- or third-line approach to the treatment of pancreatic cancer that had progressed after first-line treatment with a gemcitabine-containing regimen." Ex. 1009, 94. Cantore teaches

> [p]atients received oxaliplatin 60 mg/m^2, administered as a 2-hour intravenous infusion on days 1 + 15, followed by irinotecan 60 mg/m^2, given as a 30-min intravenous infusion on days 1 + 8 + 15. Treatment cycles were repeated every 4 weeks. If a patient responded to therapy, treatment could be continued until there was evidence of toxicity or disease progression.

Id. Cantore teaches the "combination of "irinotecan plus oxaliplatin is a well-tolerated second- or third-line systemic treatment that shows evidence of being therapeutically beneficial, in patients with progressive metastatic pancreatic cancer." *Id*. at 97. Cantore teaches the "camptothecan derivative irinotecan and the diaminocyclohexane platinum compound oxaliplatin have shown cytotoxic synergism in vitro and in vivo, with no overlapping toxicity." *Id*. at 96.

9. *Masi (Ex. 1012)*

Masi is a scientific paper published in 2004 reporting on a "phase II study to evaluate the safety and the activity of a simplified biweekly FOLFOXIRI regimen with slightly reduced doses of irinotecan and oxaliplatin and a continuous, rather than chronomodulated, infusion of 5-FU." Ex. 1012, 1767. Masi teaches the

> treatment planned consisted of: irinotecan 165 mg/m2 in 250 ml of NaCl 0.9% over 1 h, followed immediately by oxaliplatin 85 mg/m2 in 250 ml dextrose 5% and l-LV 200 mg/m2 in 250 ml dextrose 5%, infused concomitantly over 2 h via a Y-connector, followed immediately by 5-FU 3200 mg/m2 infused as a 48-h continuous infusion.

Id. at 1768. Masi teaches "[t]reatment was repeated every 2 weeks." *Id.*

Masi also teaches "this simplified FOLFOXIRI combination has manageable toxic effects and very promising antitumor activity. While the safety profile seems to be improved in comparison with our previous FOLFOXIRI regimen, the antitumor activity and efficacy seem to be maintained." *Id*. at 1771.

10. *Ginocchi (Ex. 1016)*

> Ginocchi is an abstract from a meeting published in 2012 reporting the tolerability and activity of a modified (m) FOLFOXIRI regimen in metastatic or locally advanced pancreatic cancer patients. The regimen included a lower dose of irinotecan (administered at 150 mg/sqm on day 1 every 14 days) and of infusional 5-fluorouracil (2800 mg/sqm administered as a 48-hour continuous infusion on days 1 to 3 every 14 days). Folinic acid and oxaliplatin remained unchanged.

Ex. 1016, 1. Ginocchi teaches the "mFOLFOXIRI regimen as we used resulted feasible and quite well tolerated and it maintained its good activity in metastatic pancreatic cancer." *Id.*

11. *Carnevale (Ex. 1013)*

Carnevale is a scientific review published in December of 2015 that focuses "on the development and clinical evaluation of MM-398, a novel nanoliposomal irinotecan, which, based on recent clinical results, is now being incorporated into standard treatment paradigms for patients with advanced pancreatic cancer." Ex. 1013, 453. Carnevale teaches "the safety and toxicity profile of MM-398 appears to be comparable to, if not better than, that of irinotecan." *Id*. at 461. Carnevale teaches "[i]t is also of interest whether the optimized PK and safety profile of MM-398 over standard irinotecan would make it an ideal substitute for irinotecan in the first-line FOLFIRINOX." *Id*. at 462.

12. *Dean (Ex. 1014)*

Dean is a scientific abstract published in February 2016 reporting a trial that "is a randomized, efficacy study of a nal-IRI + 5-FU/LV + oxaliplatin regimen." Ex. 1014, 3. Dean notes that "[t]wo combination chemotherapy regimens have emerged as standard of care options for first-

line treatment of mPAC: 5-fluorouracil (5-FU)/leucovorin (LV) + irinotecan + oxaliplatin (FOLFIRINOX), and nab-paclitaxel + gemcitabine. Nal-IRI (MM-398) is a nanoliposomal formulation of irinotecan." *Id.* at 2.

B. Ground 1 – Asserted Obviousness over Conroy, Conroy Protocol, Conroy Appendix, Mahaseth, Bayever, Saif, Ko, and Cantore

1. *Petitioner's Position*

Petitioner asserts that based on our claim interpretation above, for grounds 1 and 2, "the Challenged Claims would have an effective filing date of August 21, 2015, the filing date of the '552 patent's earliest provisional application." Pet. 36.

Petitioner asserts:

> Conroy, Conroy Protocol, Conroy Appendix and Mahaseth disclose:
>
> The FOLFIRINOX method of treating metastatic adenocarcinoma of the pancreas in a human patient who has not previously received an antineoplastic agent to treat the metastatic adenocarcinoma of the pancreas (Ex. 1003, 1; Ex. 1004, 4; Ex. 1017, 1; Ex. 1005, 1), the method comprising administering an antineoplastic therapy to the patient once every two weeks (Ex. 1003, 1; Ex. 1004, 5; Ex. 1005, 1), the antineoplastic therapy consisting of:
>
> - 60 mg/m^2 oxaliplatin (Ex. 1003, 4; Ex. 1004, 16-18; Ex. 1017, 3-7),
> - 400 mg/m^2 of the (l+d) racemic form of leucovorin (Ex. 1003, 1; Ex. 1004, 14, 40; Ex. 1005, 2; Ex. 1017, 3), and
> - 2,400 mg/m^2 5-fluorouracil (Ex. 1003, 1; Ex. 1004, 5; Ex. 1005, 2);
>
> to treat the metastatic adenocarcinoma of the pancreas in the human patient. (Ex. 1003, 1; Ex. 1004, 4; Ex. 1005, 1; Ex. 1017, 1).

Pet. 40. Petitioner acknowledges that these references "used free irinotecan instead of liposomal irinotecan." *Id.* at 41.

> To address this difference, Petitioner asserts that Bayever teaches
>
> administering an antineoplastic therapy to the patient once every two weeks ([Ex. 1006], 4, 6), the antineoplastic therapy consisting of:
>
> - 60 mg/m^2 of liposomal irinotecan (*id*. at 4, 39–42),
> - 400 mg/m^2 of the (l+d) racemic form of leucovorin (*See, e.g., id*. at 4, 6, 14), and
> - 2,400 mg/m^2 5-fluorouracil (*See id.*)*;*
>
> to treat the metastatic adenocarcinoma of the pancreas in the human patient. (*Id.* at 3–4.)

Pet. 40–41. Petitioner further asserts that Saif and Ko "disclose that MM-398 liposomal irinotecan should be further evaluated to replace free-irinotecan in FOLFIRINOX in first-line therapy for metastatic pancreatic cancer." *Id.* at 41.

Petitioner asserts that Cantore, the Conroy Protocol, and the Conroy Appendix "disclose that 60 mg/m^2 oxaliplatin was safe and effective in treating metastatic pancreatic cancer when administered with irinotecan every two weeks. (Ex. 1003, 1; Ex. 1004, 16–18; Ex. 1017, 3–7.)." *Id.* at 41.

> Petitioner asserts that
>
> the POSA would have been motivated to replace free-irinotecan with liposomal irinotecan in view of Bayever, which by then had already disclosed a method of treating metastatic pancreatic cancer with the same liposomal irinotecan composition of the Challenged Claims along with the exact same claimed doses of leucovorin and 5-FU. (Ex. 1002, ¶¶235-240 (explaining the prior arts' motivations to substitute MM-398 for the free irinotecan and the obviousness of arriving at the claimed dose, which was taught by the art).) This is further supported by Saif and Ko—not discussed during prosecution—which both suggested evaluating

> MM-398 liposomal irinotecan in first-line therapy. Ko states that MM-398 should be explored in additional studies "in the first-line setting," and then specifically references "FOLFIRINOX as a front-line standard in patients with good performance status." (Ex. 1008, 5.) Saif goes even further: first by asking that "[n]ow that we have…FOLFIRINOX as an option for first-line treatment, how will this [MM-398] regimen fit in the algorithm of the treatment," and then answering "[i[t seems logical to test this [MM-398] drug/regimen further" to determine "replacing irinotecan in FOLFIRINOX with MM-398." (Ex. 1007, 1.) Thus, contrary to Patent Owner's arguments during prosecution, the prior art clearly provided motivation to combine the MM-398 liposomal irinotecan of Bayever with the gold-standard first-line therapy of FOLFIRINOX.

Pet. 42–43. Petitioner further asserts that Mahaseth "teaches a modified FOLFIRINOX regimen that eliminates the 400 mg/m^2 bolus" and that "the [https://search.docketnavigator.com/patent/document/2223127] Conroy Protocol and Appendix disclosed numerous instances of oxaliplatin dose reductions to 60 mg/m^2 based on various toxicity events, which a POSA would have readily understood." *Id.* at 43–44 (citing Ex. 1003, 4; Ex. 1004, 16–18; Ex. 1017, 3–7; Ex. 1002 ¶¶ 97, 105–106, 241–242.)

Petitioner also cites Dr. Ratain's testimony that "lowering the dose of oxaliplatin from 85 mg/m^2 to the claimed 60 mg/m^2 would have been routine optimization." *Id.* at 47 (citing Ex. 1002 ¶ 241). Petitioner asserts "the Challenged Claims do not require any clinical efficacy." *Id.* at 49.

Petitioner further asserts that the results presented during prosecution that reduced dosages were better tolerated by patients were "hardly unexpected, since it has been universally accepted now and in the prior art that providing lower doses of these chemotherapy drugs results in fewer side effects." *Id.* at 51 (citing Ex. 1002 ¶¶ 69–82, 253–262).

Petitioner separately addresses independent claim 12, as well as the timing limitations of claims 3–6, 11, 13, and 14, the specific liposomal composition encapsulating irinotecan limitations of claims 8–10. Pet. 53–58.

2. *Patent Owner's Position*

a. Conroy Protocol - Translation

Patent Owner asserts that Petitioner's grounds all rely upon the "Conroy Protocol (Ex. 1004), which is written in a language other than English and for which CSPC has provided no certified translation. CSPC's failure to provide a certified translation of the Conroy Protocol violates 37 C.F.R. § 42.63, which governs the form of evidence in *inter partes* review proceedings." Prelim. Resp. 16. Patent Owner asserts the "Conroy Protocol is a French language document, but Petitioners have not filed any certification attesting to the accuracy of the translation." *Id.* at 17. Patent Owner asserts that Petitioner's "failure to comply with 37 C.F.R. § 42.63 removes the Conroy Protocol from consideration as evidence" and therefore "the Conroy Protocol should be accorded no weight in this proceeding." *Id*. at 18.

Patent Owner also asserts Petitioner's "purported translation of the Conroy Protocol contains apparent discrepancies and/or ambiguities that cast doubt on its accuracy. [Petitioner] relies on the Conroy Protocol solely for its alleged disclosure of 60 mg/m^2." *Id.* at 19. Patent Owner asserts that in the portion of the Conroy Protocol cited by Petitioner "as disclosing dose reduction of oxaliplatin, [Petitioner]'s purported translation omits a symbol critical to understanding the supposed basis for such dose reduction [oxaliplatin]." *Id*. Patent Owner asserts that Petitioner's "purported

translation of the Conroy Protocol also appears to reflect discrepancies and/or ambiguities in formulas for calculating oxaliplatin dose intensity." *Id.*

b. Conroy Protocol and Conroy Appendix – Publicly Accessible Prior Art

Patent Owner asserts Petitioner "fails to establish that either the Conroy Protocol or the Conroy Appendix is a prior-art printed publication." Prelim. Resp. 20–21. Patent Owner notes that Petitioner "bears the burden of establishing that the Conroy Protocol and the Conroy Appendix—references upon which CSPC relies for each of its asserted grounds of obviousness—qualify as prior art." *Id.* at 21. Patent Owner asserts "[n]either the Conroy Protocol nor the Conroy Appendix contains a publication date on its face." *Id.* at 22. Patent Owner asserts the

> only other information that CSPC identifies regarding the alleged publication dates of the Conroy Protocol and the Conroy Appendix is a statement in a *separate exhibit*—Conroy (Ex. 1003)—that "[t]he protocol, including the statistical analysis plan, is available with the full text of this article at NEJM.org." *See* Paper 1, at 16 (quoting Ex. 1003 at 3). CSPC otherwise identifies nothing to establish that either the Conroy Protocol or the Conroy Appendix was publicly accessible as of the effective date, much less evidence that a POSA could have reasonably found the website and then found these references.

Id.

c. Obviousness

Patent Owner asserts that Petitioner must show the obviousness of four different "modifications, namely: (1) replacement of free irinotecan with liposomal irinotecan; (2) change in dosage from 180 mg/m^2 of free irinotecan to a dosage of 60 mg/m^2 of liposomal irinotecan; (3) reduction of

85 mg/m^2 oxaliplatin to 60 mg/m^2 oxaliplatin; and (4) removal of the bolus dose of 5-FU." Prelim. Resp. 23–24.

(1) Hindsight

Patent Owner asserts Petitioner "entirely fails to explain why a POSA would have ignored other prior art treatment options in favor of the multiple, specific modifications to FOLFIRINOX." Prelim. Resp. 24. Patent Owner asserts that a

> POSA would have been aware of such approaches, which included radiation therapy and personalized treatment options. *See, e.g.*, Ex. 2006 (Rossi) at 5, Table 3. Approaches such as immune-mediated therapies, as well as drugs designed to disrupt the tumor-stromal compartment and to take advantage of genetic defects in DNA repair, were also under investigation. *See* Ex. 2007 (Valsecchi) at 4-5, 10. Against this backdrop (which CSPC and Dr. Ratain ignore), a POSA would not have necessarily been motivated to pursue systemic chemotherapy, let alone FOLFIRINOX, let alone the specific modifications to FOLFIRINOX upon which CSPC relies.

Id. at 25.

(2) Motivation

Patent Owner asserts Petitioner "identifies no motivation to depart from FOLFIRINOX's established 'gold standard' of care, much less in the multiple, specific ways that would have been necessary in order to arrive at the claimed invention." Prelim. Resp. 26. Patent Owner asserts Petitioner "fails to establish that toxicity concerns would have prompted a POSA to make the combination of ***all four*** of these allegedly obvious modifications at once." *Id.* at 27.

Patent Owner asserts that a "POSA would have also been aware of approaches to addressing toxicity concerns by removing a chemotherapy

drug (e.g., oxaliplatin) from FOLFIRINOX's four-drug combination" and therefore a "POSA would have been motivated to subtract—rather than replace, as CSPC argues—chemotherapy drug components of FOLFIRINOX." *Id*. at 29.

Patent Owner asserts the "Dr. Ratain agrees that toxicity concerns would have motivated a POSA to pursue modifications that would not have led to the '552 patent's claimed combination therapy. The only allegedly motivating factor that Dr. Ratain cites for his obviousness opinion is that FOLFIRINOX was known to present toxicity concerns." *Id*. at 30 (citing Ex. 1002 ¶¶ 65–67). Patent Owner asserts that "Dr. Ratain's own cited references suggest removing—as opposed to replacing—chemotherapy drug components of FOLFIRINOX." *Id.* at 31. Patent Owner asserts "by Dr. Ratain's own admission, toxicity concerns would have motivated a POSA to pursue then-known modifications to FOLFIRINOX, none of which lead to the claimed invention." *Id.*

Patent Owner asserts Petitioner "identifies no legitimate motivation for a POSA to introduce liposomal irinotecan to the FOLFIRINOX regimen." *Id.* at 32. Patent Owner asserts that the "fact that components of the claimed invention were, individually, known at the time of invention does not supply requisite motivation for the claimed combination." *Id.* (*citing Personal Web Techs., LLC v. Apple, Inc*., 848 F.3d 987, 993–94 (Fed. Cir. 2017)). Patent Owner also asserts Petitioner

> fails to identify any problem that would have motivated a POSA to turn to liposomal irinotecan on the basis of these properties, let alone in combination with the other recited components of the invention. That the claimed combination was later found to provide a benefit over other therapies cannot suffice as requisite motivation.

Id. at 34 (*citing Insite Vision Inc. v. Sandoz, Inc*., 783 F.3d 853, 859 (Fed. Cir. 2015)). Patent Owner specifically asserts neither Petitioner "nor Dr. Ratain cites any motivation to introduce liposomal irinotecan to the FOLFIRINOX regimen in the specifically claimed dosage of 60 mg/m^2." *Id.* Patent Owner asserts that "Saif and Ko suffer from the same deficiency as Bayever in this regard, because neither concerns a combination therapy that includes oxaliplatin." *Id.* at 35.

(3) Expectation of Success

Patent Owner asserts that Petitioner

> and Dr. Ratain cite Conroy's disclosure of "a median relative dose intensity of oxaliplatin of 78% of the 85 mg/m^2" in support of the allegedly obvious dose reduction. *See* Paper 1 at 16. But 78% of 85 mg/m^2 is 66.3 mg/ m^2, not the claimed 60 mg/m^2. Neither CSPC nor Dr. Ratain attempts to address this discrepancy. To the extent Conroy informs what would have constituted "routine experimentation" of a result-effective variable, it would not lead a POSA to the claimed dosage of oxaliplatin.

Prelim. Resp. 37. Patent Owner also asserts that Petitioner's "argument that oxaliplatin is a 'result-effective variable' subject to routine experimentation ignores the multivariate nature of the claimed invention and relevant field." *Id*. at 38. Patent Owner asserts that the "relationship between dosage and clinical effect is not straightforward. As one publication coauthored by Dr. Ratain acknowledges, inter-patient variability in response to chemotherapy drugs produces unpredictable clinical effects." *Id*. (citing Ex. 2023, 2).

Patent Owner asserts that the "literature, including publications by Dr. Ratain, recognize that components of FOLFIRINOX present inter-patient variability in tolerance and clinical effect. Dr. Ratain's patent

describes that irinotecan is associated with inter-patient variability." *Id.* at 39 (citing Ex. 2024, 1:26–2:24). Patent Owner asserts the literature supports the position that "dose adjustments to the components of FOLFIRINOX do not yield predictable effects" and that "inter-patient variability in response to single-drug chemotherapy regimens are further unpredictable in the context of combination chemotherapy regimens." *Id.* at 39–40. Patent Owner also asserts "[a]s can be seen in the very section of the Conroy Protocol that [Petitioner] cites, toxicity events that call for a dose reduction of oxaliplatin . . . *also* call for dose reductions in other components." *Id.* at 41.

Patent Owner asserts "the unpredictability of cancer treatment and extremely low success rate for new treatments undermines any claim of reasonable expectation of success." *Id*. at 43. Patent Owner states that one "of Dr. Ratain's publications states that 'it clear that phase II oncology trials have a high negative predictive value ***but a low positive predictive value***,' where '[p]ositive predictive value is the likelihood of approval (for a disease) given a positive phase II trial (i.e., exceeding threshold response rate).'" *Id.* at 45 (citing Ex. 2010, 1).

(4) Unexpected Results

Patent Owner presents, as objective indicia of nonobviousness, an argument that its claimed regimen produces unexpected results. Patent Owner asserts that a number of publications "suggest the superiority of the '552 patent's NALIRIFOX regimen over FOLFIRINOX." Prelim. Resp. 50. During prosecution, Patent Owner submitted evidence to assert that "[i]ndeed, none of the references teach or suggest tolerability *and* efficacy of 60 mg/m^2 oxaliplatin in combination with the claimed liposomal irinotecan, oxaliplatin, leucovorin, and 5-FU dosages." *Id*. at 46 (citing Ex. 1119, 149–

150). Patent Owner asserts that "the 'post-filing' status of such evidence does not render it immaterial to patentability of the claimed methods. As the Federal Circuit has held, 'patentability may consider all of the characteristics possessed by the claimed invention, whenever those characteristics become manifest.'" *Id.* at 47 (*citing Sanofi-Aventis Deutschland GmbH v. Glenmark Pharms. Inc*., USA, 748 F.3d 1354, 1360 (Fed. Cir. 2014)).

Patent Owner asserts that neither of Petitioner's "cited references even purport to establish—as CSPC argues—that NALIRIFOX has 'identical efficacy' to FOLFIRINOX. Nichetti reflects a review and meta-analysis, 'with all the inevitable limitations' inherent to such a study, of data from a number of different clinical trials involving different regimens for treatment of pancreatic cancer." *Id.* at 48 (citing Ex. 1010, 9, 10).

3. *Analysis*

a. Conroy Protocol – Translation

While Petitioner averred in the Petition that the Conroy Protocol as submitted was a certified translation (Pet. 5), Petitioner did not submit the certification itself until June 23, 2025. *See* Ex. 1204. However, Exhibit 1204 is three different translator certifications for three different portions of the Conroy Protocol, with the first dated January 13, 2025 and the remaining two dated January 14, 2025. All of these dates are prior to the filing of the petition by Petitioner on January 17, 2025.

On the current record, Patent Owner has not identified any prejudice based on the delayed submission of the certification(s) of translation as Patent Owner had an option to seek to file a surreply in order to address this evidence. *See Belden Inc. v. Berk–Tek LLC*, 805 F.3d 1064, 1081 (Fed.

Cir. 2015)(noting that patent owners have the option to move for a surreply to address new evidence).

Accordingly, we find that the requirement for certification of the translation of the Conroy Protocol has been satisfied sufficiently to permit institution of a trial proceeding. Patent Owner, if they wish, may provide more context, objections and/or arguments during a trial proceeding on this issue.

b. Conroy Protocol and Conroy Appendix – Publicly Accessible Prior Art

To qualify as a "printed publication," a reference "must have been sufficiently accessible to the public interested in the art" before the critical date. *In re Cronyn*, 890 F.2d 1158, 1160 (Fed. Cir. 1989). Whether a reference is publicly accessible is determined on a case-by-case basis dependent on the "facts and circumstances surrounding the reference's disclosure to members of the public." *In re Lister*, 583 F.3d 1307, 1311 (Fed. Cir. 2009) (*quoting In re Klopfenstein*, 380 F.3d 1345, 1350 (Fed. Cir. 2004)). "A reference is considered publicly accessible if it was 'disseminated or otherwise made available to the extent that persons interested and ordinarily skilled in the subject matter or art[,] exercising reasonable diligence, can locate it.'" *Id.*

On this preliminary record, we find the evidence supports the public accessibility of both the Conroy Protocol and Conroy Appendix. Conroy states that "[i]n the event of predefined toxic events, protocol-specified treatment modifications were permitted (see the Supplementary Appendix, available at NEJM.org)." Ex. 1003, 3. Conroy also states "[t]he protocol, including the statistical analysis plan, is available with the full text of this

article at NEJM.org. The first author vouches for the fidelity of the study to the protocol." *Id.*

Both of these statements are reasonably understood to demonstrate that the Conroy Protocol and the Conroy Appendix were published on the New England Journal of Medicine website at the same time as the Conroy paper, and that these materials were publicly accessible to interested readers. The specific searchable website location is listed in Conroy as NEJM.org. This evidence is sufficient to satisfy Petitioner's initial burden to demonstrate that these materials were printed publications that were publicly accessible as of the publication of the Conroy paper.

Patent Owner provides no evidence in rebuttal that would demonstrate that either the Conroy Protocol and/or the Conroy Appendix were either not published along with Conroy or that these documents were not publicly accessible as links at the NEJM.org website.

Accordingly, on the current record, we find that the Conroy Protocol and the Conroy Appendix are printed publications that may be relied upon in *inter partes* review proceedings.

c. Asserted Obviousness

On the current record, we find that the evidence better supports Petitioner's position.

(1) Hindsight and Motivation

Conroy teaches treatment of patients with "measurable metastatic pancreatic adenocarcinoma that had not previously been treated with chemotherapy." Ex. 1003, 1818. Conroy initiates treatment with

> oxaliplatin at a dose of 85 mg per square meter, given as a 2-hour intravenous infusion, immediately followed by leucovorin at a

> dose of 400 mg per square meter, given as a 2-hour intravenous infusion, with the addition, after 30 minutes, of irinotecan at a dose of 180 mg per square meter, given as a 90-minute intravenous infusion through a Y-connector. This treatment was immediately followed by fluorouracil at a dose of 400 mg per square meter, administered by intravenous bolus, followed by a continuous intravenous infusion of 2400 mg per square meter over a 46-hour period every 2 weeks.

Id. at 1819. However, Conroy notes that for "predefined toxic events, protocol-specified treatment modifications were permitted." *Id.* The Conroy Protocol describes a modification for patients with PNN less than 1.5 x 10^9/L as receiving a reduced dosage of irinotecan of 150 mg/m^2, receiving a reduced dosage of oxiplatin at 60 mg/m^2 and eliminating the bolus of 5-fluorouracil. Ex. 1004, 16; Ex. 1002 ¶ 245.

Dr. Ratain states that this evidence indicates "that a significant portion of the patients undergoing the FOLFIRINOX trial were reduced to 60 mg/m^2 based on various toxicity events." Ex. 1002 ¶ 105. Therefore, Conroy and the Conroy Protocol describe a treatment protocol for some pancreatic cancer patients that differs from claim 1 of the '552 patent solely in the type of irinotecan administered.

Dr. Ratain states that "a POSA would have been aware of both irinotecan (also known as free irinotecan, CPT-11, or Camptosar) and liposomal irinotecan and understood that liposomal irinotecan may be superior to irinotecan." Ex. 1002 ¶ 83. Dr. Ratain states regarding liposomal irinotecan (MM-398) that

> preclinical studies of MM-398 suggested it was superior to irinotecan. For example, MM-398 was known to have an extended plasma half-life and higher intratumoral deposition compared with free irinotecan. (Ex. 1058; Ex. 1008 at 2, 5.) MM-398 also demonstrated increased efficacy and tolerable toxicity

> when compared with free irinotecan in an orthotopic pancreatic cancer mouse model. (*Id*.; Ex. 1059; Ex 1006 at 25.)

Ex. 1002 ¶ 91. Bayever, in the context of treatment of pancreatic cancer, confirms that the

> liposomal formulation of irinotecan has several attributes that may provide an improved therapeutic index. The controlled and sustained release improves activity of this schedule-dependent drug by increasing duration of exposure of tumor tissue to drug, an attribute that allows it to be present in a higher proportion of cells during the S-phase of the cell cycle, when DNA unwinding is required as a preliminary step in the DNA replication process. The long circulating pharmacokinetics and high intravascular drug retention in the liposomes can promote an enhanced permeability and retention (EPR) effect. EPR allows for deposition of the liposomes at sites, such as malignant tumors, where the normal integrity of the vasculature (capillaries in particular) is compromised resulting in leakage out of the capillary lumen of particulates such as liposomes. EPR may thus promote site-specific drug delivery of liposomes to solid tumors. EPR of MM-398 may result in a subsequent depot effect, where liposomes accumulate in tumor associated macrophages (TAMs), which metabolize irinotecan, converting it locally to the substantially more cytotoxic SN-38. This local bioactivation is believed to result in reduced drug exposure at potential sites of toxicity and increased exposure at cancer cells within the tumor.

Ex. 1006, 9. Bayever also teaches that "liposomal irinotecan is administered to patients . . . homozygous for the UGT1A1 *28 allele on day 1 of cycle 1 at a dose of 60 mg/m^2 and on day 1 of each subsequent cycle at a dose of ranging from 60 mg/m^2 to 80 mg/m^2." Ex. 1006, 3 (*cf*. Ex. 1006, 25, 26).

Ko, also in the treatment of pancreatic cancer context, teaches that

> PEP02 (also known as MM-398) is irinotecan sucrosofate encapsulated in a liposome drug delivery system. This stable nanoliposomal formulation has been shown in preclinical studies to improve pharmacokinetics and tumour bio-distribution of both irinotecan and its active metabolite SN-38 when compared with

> the free form of the drug, with less accumulation in many of the target organs associated with toxic side effects. PEP02 also demonstrated increased efficacy and tolerable toxicity when compared with free irinotecan in an orthotopic pancreatic cancer mouse model (Hann *et al*, 2007). The favourable pharmacokinetics of irinotecan and SN-38 after PEP02 was confirmed in the first-in-human phase 1 trial for refractory solid tumours, in which the maximum tolerated dose of PEP02 given every 3 weeks was determined as 120 mg m^2.

Ex. 1008, 921.

While we are aware that hindsight bias may plague determinations of obviousness, *Graham*, 383 U.S. at 36, we are also mindful that the Supreme Court has clearly stated that the "combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results." *KSR*, 550 U.S. at 416.

The evidence of record shows the prior art provides specific reasons to replace irinotecan with liposomal irinotecan in the treatment of pancreatic cancer, including improved sustained release, local bioactivation, increased efficacy, and reduced side effects. Ex. 1006, 9; Ex. 1008, 921; Ex. 1002 ¶¶ 91, 238, 239. These specific reasons, as supported by Dr. Ratain, provide specific support for the obviousness of modifying the Conroy Protocol for patients with toxicity to substitute a 60 mg/m^2 dose of liposomal irinotecan for irinotecan, particularly in patients with the particular UGT1A1 allele identified by Bayever. Ex. 1006, 3.

(2) Expectation of Success

We appreciate Patent Owner's point that "hope that a potentially promising drug will treat a particular cancer is not enough to create a reasonable expectation of success in a highly unpredictable art." *OSI Pharm., LLC v. Apotex Inc*., 939 F.3d 1375, 1385 (Fed. Cir. 2019).

However, on the current record, Conroy teaches the four drug treatments, using solely irinotecan rather than liposomal irinotecan, results in "an effective first-line treatment option for patients with metastatic pancreatic adenocarcinoma and good ECOG performance status." Ex. 1003, 1822. Conroy teaches the "median overall survival was significantly prolonged, with an increase of 4.3 months in the FOLFIRINOX group as compared with the gemcitabine group (11.1 vs. 6.8 months)." *Id.*

Mahaseth also teaches that Conroy's four-drug protocol but without the bolus fluorouracil treatment "is well tolerated and has significant activity in metastatic PC. In patients with stage II or III disease, treatment with modified FOLFIRINOX followed by concurrent chemoradiotherapy appears to have promising activity with respect to resectability and survival." Ex. 1005, 1315.

Saif further demonstrates an expectation that substitution of liposomal irinotecan for irinotecan will likely succeed in treatment of metastatic pancreatic cancer patients, teaching "the combination of MM-398 with 5-fluorouracil (5-FU) and leucovorin achieved an overall survival of 6.1 months, a 1.9 month improvement over the 4.2 month survival demonstrated by the control arm of 5-FU and leucovorin alone." Ex. 1007, 1. Ko similarly shows the efficacy of liposomal irinotecan, teaching "results of this clinical trial are encouraging enough to warrant moving ahead with a larger study in a similar patient population, currently ongoing as an international randomized phase 3 trial called NAPOLI-1." Ex. 1008, 924.

Consequently, unlike in *OSI*, there is significant evidence of record to support Dr. Ratain's statement that a "POSA would also know that the

combination disclosed in Bayever had been successful as based on Saif." Ex. 1002 ¶ 238.

(3) Unexpected results

We acknowledge that post-filing evidence may be used to demonstrate unexpected results. *See Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc*., 655 F.3d 1291, 1308 (Fed. Cir. 2011). However, "[a]lthough secondary considerations must be taken into account, they do not necessarily control the obviousness conclusion." *Pfizer, Inc. v. Apotex, Inc*., 480 F.3d 1348, 1372 (Fed. Cir. 2007). In asserting unexpected results as a defense against obviousness, the burden of persuasion is on Patent Owner to demonstrate that the results are unexpected compared to closest the prior art. *See Bristol-Myers Squibb Co. v. Teva Pharms. USA, Inc*., 752 F.3d 967, 977 (Fed. Cir. 2014).

On the current record, we find that balancing the asserted evidence of unexpected results with the evidence of obviousness, supports Petitioner's position that the claims would have been obvious over the prior art.

For example, Patent Owner points to a statement made during prosecution that "none of the references teach or suggest tolerability *and* efficacy of 60 mg/m^2 oxaliplatin in combination with the claimed liposomal irinotecan, oxaliplatin, leucovorin, and 5-FU dosages." Prelim. Resp. 46 (citing Ex. 1119, 149–150). However, in this argument during prosecution, the applicant failed to even acknowledge that the Conroy Protocol expressly suggested reducing the dose to 60 mg/m^2 oxaliplatin in cases where toxicity was a concern. Ex. 1004, 16. That is, this unexpected results argument made to the Examiner failed to address all the art's relevant teachings. *See* Ex. 1119, 180, 308–395.

Patent Owner's other evidence on this record does not demonstrate a difference in kind rather than a difference in degree of treatment by substituting the liposomal irinotecan as suggested by several of the prior art references including Bayever and Ko and stated by Dr. Ratain. Ex. 1006, 9; Ex. 1008, 921; Ex. 1002 ¶¶ 91, 238, 239. For example, Patent Owner asserts that in a "study abstract, the NALIRIFOX regimen in the NAPOLI 3 trial 'showed numerically improved OS [(overall survival)] compared to [FOLFIRINOX], including [modified FOLFIRINOX], in the real-world setting.' Ex. 2031 (Cockrum)." Prelim. Resp. 50. However, Cockrum[14] does not clearly state that the results of the NAPOLI 3 trial differ in kind rather than degree from those of first line FOLFIRINOX, instead only stating "NALIRIFOX regimen in the NAPOLI 3 trial showed numerically improved OS [overall survival] compared to FFX, including mFFX, in the real-world setting. Analysis adjusting for baseline characteristics are warranted and will provide further insights for the comparative efficacy of the two regimens." Ex. 2031, 1.

We recognize Patent Owner's citation of Jiao[15] as finding "NALIRIFOX was associated with better PFS (progression-free survival) (8.9 months vs. 6.8 months) and an improvement in life year gain (11.97

[14] Cockrum et al., *Overall survival (OS) of patients with metastatic pancreatic ductal adenocarcinoma (mPDAC) treated with first-line (1L) FOLFIRINOX (FFX): Bridging the gap between the NAPOLI 3 trial and real-world practice*, 43 J. Clin. Oncology, Meeting Abstract 690 (2025) (Ex. 2031).

[15] Jiao et al., Comparative effectiveness of NALIRIFOX vs. FOLFIRINOX in pancreatic cancer, 42 J. Clin. Oncology, Meeting Abstract 4160 (2024) (Ex. 2029).

months vs. 10.95 months)." Prelim. Resp. 49 (citing Ex. 2029, 1). However, Patent Owner does not present evidence that a life year gain of about one month is a difference in kind rather than merely degree or that it represents an unexpected result. As to Patent Owner's citation of Wainberg,[16] we note that Wainberg does not compare the NALIRIFOX protocol to the protocols in Conroy, but rather compares to the prior nab-paclitaxel and gemcitabine protocols. Ex. 2032, 1272. Patent Owner simply asserts the result is unexpected. We note that the statements and results within the references cited by Patent Owner are evidence, but Patent Owner's assertions and conclusions that the statements or results would have been unexpected or surprising lacks persuasive evidentiary support at this stage. "Attorney argument is not evidence. *See, e.g*., *Gemtron Corp. v. Saint-Gobain Corp*., 572 F.3d 1371, 1380 (Fed. Cir. 2009) ('[U]nsworn attorney argument . . . is not evidence')." *Icon Health & Fitness, Inc. v. Strava, Inc*., 849 F.3d 1034, 1043 (Fed. Cir. 2017).

We also note that even if there were some improvement, Dr. Ratain states

> a POSA would not have found that result to have been unexpected, since Bayever taught that liposomal irinotecan was superior to free irinotecan, and therefore a POSA would have expected the claimed regimen to be superior to FOLFIRINOX. This opinion is supported by Saif and Ko, who both were excited about such a substitution, in hopes of improving the overall survival of patients with pancreatic cancer.

[16] Wainberg et al., *NALIRIFOX versus nab-paclitaxel and gemcitabine in treatment-naive patients with metastatic pancreatic ductal adenocarcinoma (NAPOLI 3): a randomised, open-label, phase 3 trial*, 402 Lancet 1272–1281 (2023) (Ex. 2032).

Ex. 1002 ¶ 261. On the current record, Dr. Ratain's testimony is materially unrebutted.

We find that on the current record that Petitioner has demonstrated a reasonable likelihood that claims 1, 3–6, and 8–14 of the '552 patent would have been obvious over Conroy, Conroy Protocol, Conroy Appendix, Mahaseth, Bayever, Saif, Ko, and Cantore.

B. Ground 2 – Asserted Obviousness over Conroy, Conroy Protocol, Conroy Appendix, Mahaseth, Bayever, Saif, Ko, Cantore, Masi, and Ginocchi

1. *Petitioner's Position*

Petitioner asserts, as to claim 2, that

> Masi discloses that irinotecan should be administered prior to oxaliplatin in chemotherapy treatment for metastatic colorectal cancer based on the FOLFOXIRI regimen. (Ex. 1012, 5 [1770].) Ginocchi applied a modified FOLFOXIRI regimen (which administers the irinotecan before the oxaliplatin) to metastatic pancreatic patients which was shown to be well tolerated with good efficacy. (*See* Ex. 1016, 1.)

Pet. 58. Petitioner asserts that "[w]hile these references do not explicitly mention that oxaliplatin be administered 2 hours after liposomal irinotecan, this would have been merely routine optimization to determine this variable." *Id.* at 59.

Petitioner asserts as to claim 7 that the "claimed sequence of drugs is the same as FOLFOXIRI, which was shown to be safe and effective in metastatic pancreatic cancer patients." *Id.* (citing Ex. 1016, 1). Petitioner asserts as to claim 15 that "Bayever discloses administering dexamethasone, which is a corticosteroid, and an anti-emetic to the patient prior to the antineoplastic therapy." *Id.* at 60 (citing Ex. 1006, 46, 33–35; Ex. 1002 ¶¶ 310–311).

2. *Patent Owner's Position*

Patent Owner asserts, as to claim 2, that Petitioner "fails to address the fact that its lead reference teaches—contrary to the recited sequence—administration of oxaliplatin before administration of irinotecan." Prelim. Resp. 52. Patent Owner asserts that "Bayever does not support [Petitioner]'s argument, because it does not teach, suggest, or motivate the sequence of administration of oxaliplatin relative to any other drug. Indeed, the combination therapies of Bayever do not include oxaliplatin." *Id.* Patent Owner also asserts that Petitioner "does not even attempt to explain why a POSA would be motivated to apply the disclosure of Masi to a treatment regimen for a different disease and patient population, much less in combination with a different chemotherapy drug (liposomal irinotecan versus free irinotecan)." *Id.* at 53. Patent Owner asserts "Ginocchi describes a study that evaluated a modified FOLFIRINOX regimen, but does not specify the claimed sequence of administration." *Id.*

Patent Owner asserts that Petitioner's arguments for claim 7 "fail for the same reasons discussed with respect to claims 1 and 2." *Id.* at 54. Patent Owner similarly asserts that Petitioner's arguments for claim 15 "fails for the reasons already discussed with respect to Ground 1." *Id.* at 55.

3. *Analysis*

On the current record, the evidence better supports Petitioner's position.

As to claim 2, while Patent Owner correctly notes that Conroy teaches a particular order of administration, Bayever teaches, in a pancreatic cancer treatment method, that in "one embodiment, liposomal irinotecan is administered prior to 5-FU and leucovorin." Ex. 1006, 12. Bayever also

teaches "liposomal irinotecan can be administered first followed by (e.g., immediately followed by) the administration of the 5-FU and leucovorin. Such concurrent or sequential administration preferably results in liposomal irinotecan, 5-FU, and leucovorin being simultaneously present in treated patients." *Id.* at 13. Masi, in a colorectal cancer treatment, teaches "first-line irinotecan 150 mg/m^2 on day 1, oxaliplatin 65 mg/m^2 on day 2, followed by standard de Gramont schedule LV-modulated bolus plus infusional 5-FU on days 2 and 3, repeated every 2 weeks." Ex. 1012, 1770. Ginocchi similarly teaches, in a pancreatic cancer treatment, "a lower dose of irinotecan (administered at 150 mg/sqm on day 1 every 14 days) and of infusional 5-fluorouracil (2800 mg/sqm administered as a 48-hour continuous infusion on days 1 to 3 every 14 days). Folinic acid and oxaliplatin remained unchanged." Ex. 1016, 1.

On the current record, we agree that the particular timing of administration of the drugs relative to one another would have been a subject of routine optimization within the POSA's skill. This is evident from Bayever, which discloses that when there are concerns about toxicity, options include to "[s]low infusion rate by 50%." Ex. 1006, 37. Bayever notes that for patients who experience a reaction, "future infusions may be administered at a reduced rate (over 120 minutes), with discretion." *Id.*

As to claims 7 and 15, not argued by Patent Owner at this time, we find that Petitioner's argument and evidence support Petitioner's challenge on the current record.

C. *Ground 3 – Asserted Obviousness over Conroy, Conroy Protocol, Conroy Appendix, Mahaseth, Bayever, Saif, Ko, Cantore, Masi, Ginocchi, Carnevale, and Dean*

1. *Petitioner's Position*

Petitioner asserts "[u]nder Ground 3, the Challenged Claims are obvious based on an effective filing date of November 10, 2017." Pet. 60 (citing Ex. 1002 ¶¶ 312–330). Petitioner asserts that "Claim 1 is obvious for all the reasons set forth above with respect to claim 1 of Ground 1 and based on the further disclosure of Carnevale and Dean." *Id.* at 61. Petitioner asserts that "Carnevale and Dean provide even more motivation to the POSA to substitute free irinotecan with MM-398 liposomal irinotecan in the established gold-standard FOLFIRINOX regimen at the claimed doses and frequency." *Id.*

2. *Patent Owner's Position*

Patent Owner asserts "the '552 patent is entitled to an effective filing date of August 21, 2015. As such, Carnevale and Dean are not prior art." Prelim. Resp. 55–56.

3. *Analysis*

On the current record, the evidence better supports Patent Owner's position. As discussed above, we agree with Patent Owner that the claims do not require clinical efficacy. Therefore, we also agree with Patent Owner that claims 1–15 have an effective filing date of August 21, 2015, and Carnevale and Dean are not prior art. Consequently, we find that this ground of rejection relies upon references that are not prior art and therefore fails to support a finding of obviousness on the current record.

XI. CONCLUSION

After reviewing the information presented in the Petition and the

Preliminary Response, as well as the evidence of record, we determine that Petitioner has established that it is reasonably likely to succeed in establishing that claims 1–15 of the '552 patent are unpatentable.

XII. ORDER

Accordingly, it is

ORDERED that, pursuant to 35 U.S.C. § 314(a), institution of an *inter partes* review of all challenged claims on all grounds presented in the Petition is granted; and

FURTHER ORDERED that, pursuant to 35 U.S.C. § 314(a) and 37 C.F.R. § 42.4(b), notice is hereby given of the institution of a trial, which commences on the entry date of this Decision; and

FURTHER ORDERED that the trial will be conducted in accordance with a separately issued Scheduling Order.

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