

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.,
Petitioners,

v.

IPSEN BIOPHARM LTD.,
Patent Owner.

Case No. IPR2025-00505
Patent No. 11,344,552

PETITIONERS' REPLY TO PATENT OWNER'S RESPONSE

TABLE OF CONTENTS

	Page
I. INTRODUCTION	1
II. ARGUMENT	1
A. Oberstein’s Opinion Should Be Given Little to No Weight.....	1
B. Ipsen Fails to Provide Credible Evidence to Rebut Petitioner’s Arguments or the Board’s Initial Determinations on Obviousness.....	4
C. No Impermissible Hindsight Was Employed	18
D. No Unexpected Results	20
III. CONCLUSION.....	27

TABLE OF AUTHORITIES

	Page(s)
Cases	
<i>Allergan, Inc. v. Sandoz Inc.</i> , 796 F.3d 1293 (Fed. Cir. 2015)	24
<i>Am. Nat’l Mfg., Inc. v. Sleep Number Corp.</i> , IPR2019-00500, Paper 114 (PTAB Sept. 30, 2020).....	18
<i>Apotex Inc. v. Cellgene Corp.</i> , IPR2023-00512, Paper 7 (PTAB Jul. 20, 2023)	24
<i>Aventis Pharma S.A. v. Hospira, Inc.</i> , 743 F. Supp. 2d 305 (D. Del. 2010).....	22
<i>Bristol-Myers Squibb Co. v. Teva Pharms. USA, Inc.</i> , 752 F.3d 967 (Fed. Cir. 2014)	22
<i>Celltrion, Inc. v. Biogen, Inc.</i> , IPR2017-01095, Paper 60 (PTAB Oct. 4, 2018).....	7, 15
<i>Celltrion, Inc. v. Chugai Seiyaku Kabushiki Kaisha</i> , IPR2022-00578, 2023 WL 5980004 (PTAB Aug. 29, 2023).....	15
<i>In Re: Copaxone Consol. Cases</i> , 906 F.3d 1013 (Fed. Cir. 2018)	14
<i>Elekta Ltd. v. ZAP Surgical Sys., Inc.</i> , 81 F.4th 1368 (Fed. Cir. 2023)	15
<i>Gen. Elec. Co. v. Joiner</i> , 522 U.S. 136 (1997).....	3
<i>Genome & Co. v. Univ. of Chi.</i> , PGR2019-00002, Paper 40 (PTAB Apr. 14, 2020).....	6
<i>Hoffmann-LaRoche Inc. v. Apotex, Inc.</i> , 748 F.3d 1326 (Fed. Cir. 2014)	14
<i>In re Huai-Hong Kao</i> , 639 F.3d 1057 (Fed. Cir. 2011)	21

<i>ImmunoGen, Inc. v. Vidal</i> , 653 F. Supp. 3d 258 (E.D. Va. 2023), <i>aff'd sub nom. ImmunoGen, Inc. v. Stewart</i> , 130 F.4th 1328 (Fed. Cir. 2025).....	17
<i>Institut Pasteur v. Focarino</i> , 738 F.3d 1337 (Fed. Cir. 2013)	21
<i>Intell. Ventures I LLC v. T-Mobile USA, Inc.</i> , 902 F.3d 1372 (Fed. Cir. 2018)	13
<i>Janssen Pharms., Inc. v. Teva Pharms. USA, Inc.</i> , 97 F.4th 915 (Fed. Cir. 2024)	5
<i>KSR International Co. v. Teleflex Inc.</i> , 550 U.S. 398 (2007).....	5, 6, 12
<i>LKQ Corp. v. GM Glob. Tech. Operations LLC</i> , 102 F.4th 1280 (Fed. Cir. 2024)	19
<i>In re McLaughlin</i> , 443 F.2d 1392 (C.C.P.A. 1971).....	18
<i>Micron Tech., Inc. v. Yangtze Memory Techs.</i> , IPR2024-0078, 2026 WL 30880 (PTAB Jan. 5, 2026)	19
<i>In re Mouttet</i> , 686 F.3d 1322 (Fed. Cir. 2012)	15
<i>Nalpropion Pharms., Inc. v. Actavis Lab'ys FL, Inc.</i> , 934 F.3d 1344 (Fed. Cir. 2019)	16
<i>Novartis Pharms. Corp. v. West-Ward Pharms. Int'l Ltd.</i> , 923 F.3d 1051 (Fed. Cir. 2019)	12
<i>Pfizer v. Apotex</i> , 480 F.3d 1348 (Fed. Cir. 2007)	8, 16, 22
<i>Pfizer, Inc. v. Biogen, Inc.</i> , IPR2017-01168, Paper 59 (PTAB Oct. 31, 2018).....	6
<i>Prollenium US Inc. v. Allergan Industrie, SAS</i> , IPR2020-00902, 2020 WL 7251424 (PTAB Dec. 9, 2020).....	19

<i>Samsung Elecs. Co., Ltd. v. Huawei Techs. Co., Ltd.</i> , IPR2017-01487, 2018 WL 6519544 (PTAB Dec. 10, 2018).....	20
<i>Samsung Elecs. Co., Ltd. v. Netlist, Inc.</i> , IPR2022-00062, 2023 WL 5110321 (PTAB May 8, 2023).....	19
<i>In re Sebela Pat. Litig.</i> , No. 14-cv-06414, 2017 WL 3449054 (D.N.J. Aug. 11, 2017).....	24
<i>Shanghai Hongene Biotech Corp. v. Chemgenes Corp.</i> , IPR2023-00490, 2024 WL 3465176 (PTAB July 18, 2024).....	19
<i>Transclean Corp. v. Bridgewood Servs., Inc.</i> , 101 F. Supp. 2d 788 (D. Minn. 2000).....	3
<i>Varian Med. Sys. v. William Beaumont Hospital</i> , IPR2016-00169, Paper 79 (PTAB May 4, 2017)	2
<i>Wright Med. Tech., Inc. v. Osteonics Corp.</i> , 122 F.3d 1440 (Fed. Cir. 1997)	13
Other Authorities	
37 C.F.R. § 42.6(a)(3)	23
37 C.F.R. § 42.8(b)(1).....	18

UPDATED EXHIBIT LIST

Exhibit	Description
Ex. 1001	U.S. Patent No. 11,344,552 to Bayever <i>et al.</i> (“the ’552 patent”)
Ex. 1002	Declaration of Dr. Mark Ratain
Ex. 1003	Conroy, <i>et al.</i> , N. Engl. J. Med., 364(19):1817-25 (2011) (“Conroy”)
Ex. 1004	Certified English Translation of the Protocol of Conroy, <i>et al.</i> , https://www.nejm.org , ^[1] (2011) (“Conroy Protocol”)
Ex. 1005	Mahaseth, <i>et al.</i> , Pancreas, 42(8):1311-15 (2013) (“Mahaseth”)
Ex. 1006	International Publication No. WO2013/188586 A1 to Bayever (“Bayever”)
Ex. 1007	Saif, Journal of the Pancreas, 15(3):278-79 (2014) (“Saif”)
Ex. 1008	Ko, <i>et al.</i> , British J. of Cancer, 109(4):920-25 (2013) (“Ko”)
Ex. 1009	Cantore, <i>et al.</i> , Oncology, 67(2):93-97 (2004) (“Cantore”)
Ex. 1010	Nichetti, <i>et al.</i> , JAMA Network Open, 7(1):1-13 (2024) (“Nichetti”)
Ex. 1011	Nevala-Plagemann and Garrido-Laguna, Nature Reviews Clinical Oncology, 21(8):567-68 (2024) (“Nevala-Plagemann”)
Ex. 1012	Masi, <i>et al.</i> , Annals of Oncology, 15:1766-72 (2004) (“Masi”)
Ex. 1013	Carnevale and Ko, Future Oncology, 12(4):453-464 (2016) (“Carnevale”)
Ex. 1014	Dean, <i>et al.</i> , J Clin Oncol, 34(4 Suppl.):tps482 (2016) (“Dean”)
Ex. 1015	U.S. Provisional Application No. 62/208,209 to Bayever <i>et al.</i> (“the ’209 Provisional”)
Ex. 1016	Ginocchi, <i>et al.</i> , Annals of Oncology, 23(9 Suppl.):ix238 (2012) (“Ginocchi”)
Ex. 1017	Conroy Supplementary Appendix, N. Engl. J. Med., 364(19):1817-25 Supplementary Appendix (2011) (“Conroy Appendix”)

Exhibit	Description
Ex. 1018	Wainberg, <i>et al.</i> , Ann Oncol., 31 (Suppl. 3):S241 (2020) (“Wainberg abstract”), corresponding poster (“Wainberg poster”), corresponding presentation (“Wainberg presentation”)
Ex. 1019	Wainberg, <i>et al.</i> , European Journal of Cancer, 151:14-24 (2021) (“Wainberg 2021”)
Ex. 1020	U.S. Non-Provisional Patent Application No. 15/241,106 to Bayever <i>et al</i> (“the ’106 Application”)
Ex. 1021	Hatachi, <i>et al.</i> , Cancer Diagn & Progn, 2(1):101-06 (2022)
Ex. 1022	Zaniboni, <i>et al.</i> , Cancer Chemother Pharmacol., 69(6):1641-45 (2012)
Ex. 1023	Tsai, <i>et al.</i> , J Gastrointest Oncol., 2(3):185-94 (2011)
Ex. 1024	U.S. Patent No. 8,147,867 to Hong, <i>et al</i> (“the ’867 patent”)
Ex. 1025	Press Release by Merrimack Pharmaceuticals, Inc. on August 1, 2011
Ex. 1026	International Publication No. WO 2016/094402 A1 to Bayever (“Bayever II”).
Ex. 1027	Alcindor, <i>et al.</i> , Curr Oncol, 18(1):18-25 (2011)
Ex. 1028	U.S. Provisional Application No. 62/216,736 to Bayever <i>et al.</i> (“the ’736 Provisional”)
Ex. 1029	U.S. Provisional Application No. 62/273,244 to Bayever <i>et al.</i> (“the ’244 Provisional”)
Ex. 1030	U.S. Provisional Application No. 62/281,473 to Bayever <i>et al.</i> (“the ’473 Provisional”)
Ex. 1031	U.S. Provisional Application No. 62/302,341 to Bayever <i>et al.</i> (“the ’341 Provisional”)
Ex. 1032	U.S. Provisional Application No. 62/323,245 to Bayever <i>et al.</i> (“the ’245 Provisional”)
Ex. 1033	Leucovorin Calcium Injection Label (2011)
Ex. 1034	Gemcitabine Injection Label (2012)
Ex. 1035	Abraxane Paclitaxel Label (2013)

Exhibit	Description
Ex. 1036	XELODA Capecitabine Label (2000)
Ex. 1037	Camptosar FDA Label (2006)
Ex. 1038	Eloxatin Oxaliplatin Injection Label (2012)
Ex. 1039	Tarceva Erlotinib Tablets Label (2013)
Ex. 1040	Fluorouracil Injection Label (2012)
Ex. 1041	Conroy, <i>et al.</i> , Curr Oncol Rep., 15(2):182-9 (2013)
Ex. 1042	Ko, J Clin Oncol, 29(28):3727–29 (2011)
Ex. 1043	Blazer, <i>et al.</i> , ASCO Meeting Abstr. 32(Suppl. 3):275 (2014)
Ex. 1044	Alessandretti, <i>et al.</i> , ASCO Meeting Abstr. 31 (Suppl. 15): e15176 (2013)
Ex. 1045	Paller, <i>et al.</i> , Clin Cancer Res., 20(16): 4210–17 (2014)
Ex. 1046	Hamberg, <i>et al.</i> , Eur J Cancer, 46(16):2870-78 (2010)
Ex. 1047	Hess, <i>et al.</i> , Annals of Oncology, 21(12):2390-95 (2010)
Ex. 1048	Goel, <i>et al.</i> , Anti-Cancer Drugs, 18(3):263-71 (2007)
Ex. 1049	Rachamalla, <i>et al.</i> , Anticancer Drugs, 15(3):211-7 (2004)
Ex. 1050	Wildiers, Eur J Cancer, 43(15):2235-41 (2007)
Ex. 1051	Gajra, <i>et al.</i> , J Geriatr Oncol, 6(2):133-40 (2015)
Ex. 1052	Shayne, <i>et al.</i> , Cancer, 110(7):1611-20 (2007)
Ex. 1053	Sharma, <i>et al.</i> , J Clinical Oncology, 32(3 Suppl.): 562 (2014)
Ex. 1054	Chang, <i>et al.</i> , Cancer Chemother Pharmacol., 75(3):579-86 (2015)
Ex. 1055	Roy, <i>et al.</i> , Annals of Oncology, 24(6):1567-73 (2013)
Ex. 1056	Slingerland, <i>et al.</i> , Drug Discov Today, 17(3-4):160-66 (2012)
Ex. 1057	Chen, <i>et al.</i> , J Clin Oncol, 26(15 Suppl.):2565 (2008)
Ex. 1058	Kim, <i>et al.</i> , Cancer Res., 72(14 Suppl.): A41 (2012)
Ex. 1059	Hann, <i>et al.</i> , Cancer Res, 67(9 Suppl.): 5648 (2007)
Ex. 1060	U.S. Non-Provisional Patent Application No. 62/343,313 to Bayever et al (“the ’313 Provisional”)

Exhibit	Description
Ex. 1061	National Cancer Institute, “FDA Approves Irinotecan Liposome to Treat Pancreatic Cancer” ¹ (2015)
Exs. 1062 - 1083	Intentionally Omitted
Exs. 1084 - 1123	File History of U.S. Patent No. 11,344,552 Parts 1 to 40
Exs. 1124 - 1199	Intentionally Omitted
Ex. 1200	Supplemental Expert Declaration of Mark J. Ratain, MD
Ex. 1201	Chung, <i>et al.</i> , Journal of Clinical Oncology, 43(17 suppl): LBA4175 (2025)
Ex. 1202	Chung, <i>et al.</i> , NAPOLI 3 Phase 3 Trial of NALIRIFOX in Metastatic Pancreatic Ductal Adenocarcinoma: Characteristics of Long-term Survivors. Presented at ASCO Annual Meeting on May 31, 2025
Ex. 1203	Rochefort, <i>et al.</i> , The Oncologist, 24:1543-1548 (2019)
Ex. 1204	Translation Certification of the English Translation of Conroy Protocol (Ex. 1004)
Ex. 1205	U.S. Patent No. 9,492,442
Ex. 1206	NCCN Clinical Practice Guidelines for Pancreatic Adenocarcinoma published on February 3, 2025.
Ex. 1207	Patel, <i>et al.</i> , Journal of Clinical Oncology, 43(4 suppl):716 (2025)
Ex. 1208	Declaration of Howard S. Suh in Support of Motion for Admission <i>Pro Hac Vice</i>

¹ National Cancer Institute, *FDA Approves Irinotecan Liposome to Treat Pancreatic Cancer*, (Nov. 24, 2015) <https://www.cancer.gov/news-events/cancer-currents-blog/2015/irinotecan-liposome-pancreatic> (last visited Feb. 10, 2026).

Exhibit	Description
Ex. 1209	Intentionally Omitted
Ex. 1210	Dr. Oberstein Deposition Transcript
Ex. 1211	Video of Panel Interview with Dr. Oberstein, found at https://www.onclive.com/view/napoli-3-trial-deep-dive-asco-2025-updated-os-analysis , (last accessed February 9, 2026)
Ex. 1212	Page Vault Capture of Exhibit 1211 website
Ex. 1213	Transcript of Exhibit 1211 video
Ex. 1214	2024 Open Payments Records for Dr. Oberstein, accessible at https://openpaymentsdata.cms.gov/physician/284735 , (last accessed February 9, 2026).
Ex. 1215	Office of Inspector General, U.S. Dep't of Health & Human Servs., <i>Special Fraud Alert: Speaker Programs</i> (Nov. 16, 2020), https://oig.hhs.gov/documents/special-fraud-alerts/865/SpecialFraudAlertSpeakerPrograms.pdf .
Ex. 1216	Eran Sadot et al., <i>FOLFIRINOX Induction Therapy for Stage 3 Pancreatic Adenocarcinoma</i> , 22 <i>Annals of Surgical Oncology</i> 3512 (2015).
Ex. 1217	Chia Jie Tan et al., <i>Cost-Effectiveness of NALIRIFOX Compared to Other First-Line Treatments for Metastatic Pancreatic Cancer</i> , 43 <i>J. Clinical Oncology</i> (Supp. 4) 733 (2025) (abstract).
Ex. 1218	Ipsen's January 20, 2023 NCCN Guidelines Submission
Ex. 1219	NCCN's June 2023 Panel Discussions
Ex. 1220	Ipsen's September 12, 2023 NCCN Guidelines Submission
Ex. 1221	NCCN's January 2024 Panel Discussions
Ex. 1222	Affidavit of Capture of Exhibits 1211-1212

I. INTRODUCTION

The '552 Patent is invalid for obviousness because the prior art provided a clear roadmap for a person of ordinary skill in the art (POSA) to make routine, predictable modifications to the FOLFIRINOX regimen to manage its known toxicity. The prior art explicitly suggested substituting liposomal irinotecan for free irinotecan at 60 mg/m² (Saif, Ko, Bayever), reducing the oxaliplatin dose to 60 mg/m² (Conroy Protocol/Appendix), and omitting the 5-FU bolus (Conroy Protocol/Appendix, Mahaseth, Bayever). The combination of these well-documented, logical steps would have led a POSA directly to the claimed regimen. Ipsen's arguments to the contrary rely on the flawed, overly rigid opinion of its expert and unsubstantiated claims of "unexpected results," neither of which can overcome this strong case of obviousness.

II. ARGUMENT

A. Oberstein's Opinion Should Be Given Little to No Weight.

Dr. Oberstein ("Oberstein"), who previously stated the claimed treatment regimen and schedule were "quite similar" to FOLFIRINOX, (Ex. 1211², 0:10-0:25, 1:52-2:04; Ex. 1213, 1), now offers conclusory and unsupported assertions to the

² <https://www.onclive.com/view/napoli-3-trial-deep-dive-asco-2025-updated-os-analysis> (last visited February 10, 2026); Exs. 1212, 1222 (capture of same).

contrary to help Ipsen, who has been writing checks to Oberstein for years. This conflict of interest and bias warrants giving his testimony little to no weight. *See Varian Med. Sys. v. William Beaumont Hospital*, IPR2016-00169, Paper 79 at 30, (PTAB May 4, 2017) (“A financial interest is certainly a factor in deciding how much weight to give [an expert’s] testimony.”)

First, Oberstein admits that Ipsen has been paying him tens of thousands of dollars a year [REDACTED] for “consulting” services, most or all of which relate to NALIRIFOX, which is the combination regimen of the Challenged Claims. (Ex. 1214, 1-7 (showing between \$54,000-\$63,000 in payments from Ipsen in 2024 alone); Ex. 1210, 36:13-39:18, 45:7-46:21 ([REDACTED]
[REDACTED]
[REDACTED]).) Oberstein also admitted that his prescribing of NALIRIFOX has grown substantially in the last two years and is now one of his most prescribed treatments, despite it having an unacceptable cost to value and no advantage over FOLFIRINOX. (Ex. 1210, 80:5-81:16, 317:22-318:3; *infra* Section II.D.3.) Federal guidance suggests such a relationship between providers and pharmaceutical companies creates a high-risk arrangement that can inappropriately influence medical judgment. (Ex. 1215 (further explaining risks of bias).)

Second, an opinion founded on “sheer conjecture” of *ipse dixit* rather than “reliable methodolog[ies]” warrants little to no weight. *Transclean Corp. v. Bridgewood Servs., Inc.*, 101 F. Supp. 2d 788, 804 (D. Minn. 2000); *Gen. Elec. Co. v. Joiner*, 522 U.S. 136, 146 (1997)). Here, Oberstein offers conclusory opinions, supported by his *ipse dixit* or contradicted by the cited evidence, which should be given little to no weight. (*See, e.g.*, Ex. 2076, ¶¶48-50, 52-53, 60-62, 66, 76, 79, 83-84, 88-91, 93-94, 152-153, 160-161, 205-207, 212, 221, 231-234, 236, 239-242, 245-252, 254, 257-258, 261, 263-264, 275-277, 279-280, 284, 288-293, 295-296, 300, 304, 307-308, 310.)

Third, and as explained *infra* Sections II.B.1-2, II.D, Oberstein fails to properly apply the law, continues to look at each reference in isolation, refuses to acknowledge logical suggestions in the art, and imports new limitations into the claims. (*See also, e.g.*, Ex. 2076, ¶¶86-88, 271-274.) For example, Oberstein erroneously suggests a POSA would evaluate how to arrive at a new “standard of care” or that the claims were “for a patient population as a whole” (as opposed to individualized treatment or therapeutic approaches), even though these are not limitations of the claims. (*See, e.g.*, Ex. 2076, ¶¶71, 76, 86, 88, 108-109.) Similarly, Oberstein and Ipsen repeatedly argue that the Conroy Protocol/Appendix do not teach a 60 mg/m² dose of oxaliplatin or the removal of the 400 mg/m² 5-FU bolus

dose within FOLFIRINOX because this regimen recommends a *starting* dose of 85 mg/m² oxaliplatin with the 5-FU bolus, and that dose adjustments down to 60 mg/m² for oxaliplatin and the removal of the 5-FU bolus only occur when the starting dose causes certain side effects. But none of the Challenged Claims are limited to a method of treatment for a single starting dose at the first treatment cycle: they also cover subsequent administrations of these drugs in later treatment cycles. Moreover, Oberstein and Ipsen discount Bayever's disclosure of 60 mg/m² of liposomal irinotecan as an effective treatment for UGT1A1*28 homozygous patients. But, again, the claims are not limited to exclude these patients.

B. Ipsen Fails to Provide Credible Evidence to Rebut Petitioner's Arguments or the Board's Initial Determinations on Obviousness.

Ipsen's Response (POR) repeats a legally flawed and already rejected argument raised in its POPR: that the prior art would not motivate POSAs to make *four* simultaneous changes to FOLFIRINOX— replacing free irinotecan with liposomal irinotecan, dosing liposomal irinotecan at 60 mg/m², reducing the oxaliplatin dose to 60 mg/m², and removing the 400 mg/m² 5-FU bolus—to speculate that arriving at these changes would require multiple and unpredictable prior art combinations. However, the Board correctly rejected this argument when it recognized that all of these changes were disclosed by making just the *single* prior art combination of Conroy (and its Protocol) with Bayever. Paper 13 at 27-28, 34-

39. “A POSA can be motivated to do more than one thing.” *Janssen Pharms., Inc. v. Teva Pharms. USA, Inc.*, 97 F.4th 915, 930 (Fed. Cir. 2024).

As acknowledged by the Board, Conroy discloses FOLFIRINOX, which has the same active ingredients as the Challenged Claims, (Ex. 1003, 1; Ex. 1210, 208:8-209:12); Conroy’s Protocol teaches two of the changes: use of 60 mg/m² oxaliplatin and removal of the 5-FU bolus, (Ex. 1004, 16-18); and Bayever suggests three changes: benefits of liposomal irinotecan and a dose thereof of 60 mg/m² as well as foregoing a 5-FU bolus, (Ex. 1006, 4-5). (Paper 13 at 34-39.) The Board also correctly found that this combination was strongly motivated by Bayever, Ko, and Saif to replace free irinotecan in FOLFIRINOX with liposomal irinotecan because the prior art suggested that liposomal irinotecan had a *superior* efficacy and toxicity profile. (*Id.*, 35-37). Critically, Ipsen cites *no evidence* that its liposomal irinotecan (MM-398) was *inferior*.

The claimed invention was an obvious evolution of existing pancreatic cancer treatments and Ipsen’s effort to cabin the prior art’s teachings or limit a POSA’s thinking is contrary to the evidence and the flexible approach to obviousness demanded by *KSR International Co. v. Teleflex Inc.*, 550 U.S. 398, 415–18, 427–28 (2007). The obviousness analysis is “expansive and flexible” not “rigid” and must

analyze the prior art not in isolation, but rather with consideration of their “interrelated teachings.” *See id.*

In fact, it is Ipsen and Oberstein (not Petitioner) who resort to a piecemeal application of obviousness by looking at references in isolation to argue against a motivation to combine or reasonable expectation of success; arguing a particular prior art reference, such as Bayever, Ko, or Saif, does not disclose the claimed oxaliplatin dose, or that Conroy does not disclose liposomal irinotecan. (POR, 26-50.) Ipsen’s defective, anticipation-like approach, ignores that obviousness does not rely on a single reference disclosing all elements. As the Board correctly acknowledged, *KSR* demands that “the combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results.” (Paper 13 at 37 (*quoting KSR*, 550 U.S. at 416).) The Board has repeatedly invalidated cancer treatment patents based on this doctrine, as should be done here, where each of the claimed drugs within the combination was already known to treat the cancer. *See Genome & Co. v. Univ. of Chi.*, PGR2019-00002, Paper 40 at 44 (PTAB Apr. 14, 2020) (“Given the teachings of the reference that both [agents] exhibit an anti-tumor effect, we agree with Petitioner that it would have been obvious to combine the two agents to treat cancer.”); *Pfizer, Inc. v. Biogen, Inc.*, IPR2017-01168, Paper 59 at 23 (PTAB Oct. 31, 2018) (holding the claimed method simply

adds rituximab to the Moreau regimen and “amounts to no more than ‘the predictable use of prior art elements according to their established functions.’”); *Celltrion, Inc. v. Biogen, Inc.*, IPR2017-01095, Paper 60 at 55 (PTAB Oct. 4, 2018).

As explained, multi-component oncology regimens were routinely adjusted to balance toxicity and efficacy, especially in palliative situations for metastatic cancers. (Ex. 1002, ¶¶79-80; Ex. 2076, Appendix B; Ex. 1050, 2 (palliative situations are “different” and “more efforts should be made to avoid toxicity” and to “definitely consider dose modifications”).) While FOLFIRINOX was a standard of care, its severe toxicity was well-known, leading clinicians to routinely modify its components—including reducing doses of irinotecan, oxaliplatin, and 5-FU—to improve tolerability. (Ex. 2076, ¶¶58-61, 79, 88-89, 257 (Oberstein acknowledging dose reductions, including of oxaliplatin, 5-FU, and irinotecan occurred and stating modified FOLFIRINOX studies demonstrates a willingness to modify “each of the four components, including oxaliplatin and leucovorin, in order to address toxicity concerns or to treat sensitive patient populations”), Appendix B (showing over a dozen examples of modified regimens that were published or were being conducted prior to the effective date that consisted of reduced doses of two, three, or four of the FOLFIRINOX drugs); Ex. 1002, ¶¶67, 69-72, 79-80 (explaining that modifications to FOLFIRINOX were “common” and citing examples of same); Ex. 1216 (a review

of over 100 Memorial Sloan Kettering patients treated between 2010 and 2013 who received a reduced “starting dose,” “instituted at the discretion of the treating medical oncologist” of “80% of that used in [Conroy]”).)

Thus, this established practice of dose modifications and the continued need to test and develop new treatments created a clear pathway for a POSA to arrive at the claimed regimen, which would have been particularly true after the art began suggesting the substitution of free irinotecan with its less toxic liposomal irinotecan formulation, a/k/a MM-398. (Pet., 41-47; Exs. 1007-1008.) In addition, Bayever had promoted the advantages of liposomal irinotecan over free irinotecan as well as proposed a liposomal irinotecan combination with leucovorin and 5-FU at the claimed doses for each drug. (Pet., 44-45; Ex. 1006, 4-5.) Moreover, Ipsen fails to rebut that adjusting oxaliplatin's dose was routine optimization of a known, result-effective variable. (See Pet. at 48 (citing *Pfizer v. Apotex*, 480 F.3d 1348, 1368 (Fed. Cir. 2007) (finding an optimal value of a result-effective variable is “usually obvious”).)

The prior art provided a clear roadmap: substitute liposomal irinotecan for free irinotecan (Saif, Ko, Bayever), omit the 5-FU bolus (Conroy Protocol/Appendix, Mahaseth, Bayever), and reduce the oxaliplatin dose, especially

for more at risk patients (Conroy Protocol/Appendix). Following these suggestions was the logical, predictable application of known principles to a known problem.

1. A POSA Would Have Been Motivated to Combine the Art.

a. The Art Explicitly Motivated Substituting Liposomal Irinotecan for Free Irinotecan.

The art is anything but silent, (POR 35-38), as Ko, Saif, and Bayever provided direct motivation to substitute liposomal irinotecan at 60 mg/m² in FOLFIRINOX. (See Pet., 42-43; Paper 13 at 37 (Board finding same).)

First, even Oberstein admits that Ko suggests that liposomal irinotecan should be explored as “part of a combination regimen” for pancreatic cancer “in the first-line setting.” (Ex. 2076, ¶271; *see also* Ex. 1008, 5 (Ko further mentioning FOLFIRINOX as a first-line standard), 2 (also identifying various benefits to liposomal irinotecan); Ex. 1002, ¶¶235-240).) Ipsen’s and Oberstein’s conclusory assertions simply cannot overcome the plain meaning of Ko when it explicitly states that the POSA “may explore this [MM-398 liposomal irinotecan]’s role in the *first-line* setting and as part of combination regimens,” which is immediately followed by the statement that FOLFIRINOX has emerged as the “front-line standard,” and that the “utility of [MM-398]” “merits further investigation.” (Ex. 1008, 5.)

Second, Saif—which discusses a positive test of a combination of liposomal irinotecan, 5-FU, and leucovorin—asks and answers the core motivation question,

stating it “seems logical” to test whether liposomal irinotecan should replace irinotecan in FOLFIRINOX. (Ex. 1007, 1 (providing a positive example of a similar substitution before positing and answering the question).) Ipsen does not dispute this suggestion but relies heavily on Saif’s reminder that FOLFIRINOX’s known toxicities should be “borne in mind.” (POR at 17, 37; Ex. 1210, 189:9-190:17.) But POSAs were already addressing these exact toxicity concerns through dose modifications. (Pet. 34, 46-47; *supra* Section II.B; *infra* Section II.D.2 (explaining known efficacy preservation using dose reductions).)

Third, any “reminder” in Saif does not strip away the “logical” suggestion to use liposomal irinotecan in FOLFIRINOX, especially when there is no dispute that the art, including Bayever, discussed multiple benefits of liposomal irinotecan over free irinotecan and proposed using it in similar ways. (Ex. 1002, ¶¶120-129 (citing Ex. 1006 at 4-6, 10, 13-16, 19-21, 26-27, 33, 55 (describing multiple benefits and use of liposomal irinotecan with leucovorin and 5-FU on same schedule claimed by ‘522 Patent)), 206, 236 (citing Ex. 1084, 292; Ex. 1006); Ex. 1210, 225:25-226:14 (admitting Bayever teaches potential benefits of liposomal irinotecan over free irinotecan).) In fact, Bayever outright states that there is “an urgent need for improvements . . . in current therapies for pancreatic cancer” [after discussing toxicity concerns of free irinotecan] and that “[t]he disclosed [MM-398] invention

addresses this need and provides other benefits.” (Ex. 1006, 3-4 (further proposing use of 60 mg/m² dose of liposomal irinotecan as part of combination treatment).)

Finally, Ipsen's argument regarding a risk of combining irinotecan and oxaliplatin, (POR, 37), simply ignores that these drugs had already been combined, e.g., in FOLFIRINOX. (*See also* Pet. at 23-24 (citing Ex. 1015, 4; Ex. 1012, 5 and acknowledging “cytotoxic synergism[s]” including when administered at 60 mg/m²).) Ipsen presents no evidence that liposomal irinotecan would be less safe or less effective.

b. The Prior Art Would Motivate a POSA to Use 60 mg/m² Oxaliplatin and Omit the 5-FU Bolus.

A POSA “cautious” of the risk of neutropenia—as Ipsen suggests (POR, 37)—would have similarly reconsidered the oxaliplatin dose and been motivated to reduce it to 60 mg/m². Conroy reported the median dose intensity for oxaliplatin was 78%, suggesting multiple patients received a dose reduction. (Ex. 1210, 163:14-164:6, 252:23-253:11 (Oberstein agreeing that half the participants received less than 78% the prescribed 85 mg/m² dose, which is a “significant number”).) The Conroy Protocol/Appendix provided dose-reduction rules and the only reduced dose for the administration of oxaliplatin identified was 60 mg/m². (*See* Ex. 1004, 16; Ex. 1017, 4-7.) The dose-reduction criteria suggested 60 mg/m² in response to various hematological toxicities. (Ex. 1004, 16-18; Ex. 1017, 3-7; Ex. 1002, ¶105; Ex. 1003,

4.). A POSA looking to preemptively avoid some of the noted toxicity concerns—e.g., for older, frail, or UGT1A1*28 homozygous individuals—would undoubtedly consider a reduction in oxaliplatin to 60 mg/m². *See KSR*, 550 US at 418 (obviousness analysis must “take account of the inferences and creative steps that a [POSA] would employ”); *Novartis Pharms. Corp. v. West-Ward Pharms. Int’l Ltd.*, 923 F.3d 1051, 1059 (Fed. Cir. 2019) (obviousness does not “require that a particular combination must be the preferred, or the most desirable, combination described in the prior art”).

Moreover, a POSA would recognize that a dose of 60 mg/m² oxaliplatin was not only contemplated but actually used in Conroy. (Ex. 1002, ¶105; Ex. 2076, ¶242 (Oberstein admitting “dose reductions occurred during the [Conroy] course of treatment for some patients.”).) Ipsen and Oberstein insist that these dose reductions of 60 mg/m² oxaliplatin are not material because these were not starting doses. But as discussed above, none of the Challenged Claims are limited to a method of treating first-line metastatic pancreatic cancer with just a starting dose; rather, they are broad enough to cover subsequent doses and treatment cycles. After all, claim 1 requires administration of the claimed therapy “once every two weeks,” and dependent claims 5 and 11 require administration of the claimed drugs “on days 1 and 15 of a 28-day treatment cycle.” To construe the Independent Claims to be

limited to a particular starting dose, as Ipsen and Oberstein suggest, would render these dependent claims internally inconsistent and meaningless, which is highly disfavored and surely cannot be the result of a proper claim construction. *See Intell. Ventures I LLC v. T-Mobile USA, Inc.*, 902 F.3d 1372, 1378 (Fed. Cir. 2018) (construing claims to render them meaningless is highly “disfavored”); *Wright Med. Tech., Inc. v. Osteonics Corp.*, 122 F.3d 1440, 1445 (Fed. Cir. 1997) (“[W]e must not interpret an independent claim in a way that is inconsistent with a claim which depends from it.”).³ Ipsen’s reliance on Ychou, (*see* POR at 28-29), is misplaced. Ychou sought to determine the maximum tolerated and recommended doses of *free*

³ While claims 5, 11, and 13 state that the claimed drug doses are administered on “days 1 and 15 of a 28-day treatment cycle,” this does not limit the claims to only the first treatment cycle. In fact, the ’552 patent itself contemplates multiple cycles of treatment, and that “[t]he safety assessment period for purposes of DLT [dose limiting toxicities] evaluation and dose escalation decisions is one cycle of treatment [i.e. 28 days]” (Ex. 1001, 26:31-33.) Moreover, much like the starting doses of FOLFIRINOX, the target dose of the clinical trial contemplated in the ’552 patent was 85 mg/m² of oxaliplatin, where 60 mg/m² is selected if there are toxicity concerns. (*See id.* at Table 3.)

(not liposomal) irinotecan and oxaliplatin (when combined with 5-FU/LV). (Ex. 2038, 1-2.) Ychou recognized prior treatments used 85 mg/m² oxaliplatin but started the trial at 60 mg/m² oxaliplatin. (*Id.*) Ychou’s conclusion—based on a combination of oxaliplatin with free irinotecan—says nothing about any recommended dosing of oxaliplatin with *liposomal* irinotecan but would suggest to 60 mg/m² oxaliplatin as a starting point when considering a potential reduction of oxaliplatin from 85 mg/m². (*See generally id.*)

Regarding elimination of the 5-FU bolus, this too was taught in the Conroy Protocol/Appendix. (*See* Ex. 1004, 16-18 (disclosing 5-FU bolus was removed *and* oxaliplatin was reduced to 60 mg/m² when patients experienced certain side effects).) It is well recognized that such a modification was known and common. (*See* Paper 13 at 18 (citing Ex. 1005 (Mahaseth), 1311); Ex. 2076, ¶257 (bolus elimination one of “most common” reductions).).

2. A POSA Would Have a Reasonable Expectation of Success In Combining the Art.

Ipsen and Oberstein misapply the law regarding reasonable expectation of success. (POR 42-50.) A *reasonable* expectation of success “does not require absolute predictability of success,” or “conclusive proof of efficacy.” *In Re: Copaxone Consol. Cases*, 906 F.3d 1013, 1026 (Fed. Cir. 2018); *Hoffmann-LaRoche Inc. v. Apotex, Inc.*, 748 F.3d 1326, 1331 (Fed. Cir. 2014). The expectation can be

implicit and may flow from the same prior art evidence that supplies the motivation to combine. *Elekta Ltd. v. ZAP Surgical Sys., Inc.*, 81 F.4th 1368, 1376-77 (Fed. Cir. 2023). The law is “clear that a showing of reasonable expectation of success in a method of treatment claim need not rely on clinical data [nor] include a demonstration of certainty that the treatment would be successful in every instance.” *Celltrion, Inc. v. Chugai Seiyaku Kabushiki Kaisha*, IPR2022-00578, 2023 WL 5980004, at *18 (PTAB Aug. 29, 2023) (quotation omitted) (finding this “particularly true” where the claims don’t recite an “‘effective amount’ or ‘efficacy’ limitation”).

The standard applied by Oberstein for reasonable expectation of success was whether it was “more likely than not” that a POSA would expect a benefit that is statistically significant when “compared to the old regimen.” (Ex. 2010, 223:8-15, 314:24-315:20, 351:11-356:10.) The Board has rejected “mistaken” assertions that the expectation be tied to “more favorable results” than an alternative. *Celltrion*, IPR2017-01095, Paper 60 at 55. “[J]ust because better alternatives exist in the prior art does not mean that an inferior combination is inapt for obviousness purposes.” *Id.* (quoting *In re Mouttet*, 686 F.3d 1322, 1334 (Fed. Cir. 2012)).

Here, the prior art showed each component of the claimed invention had known efficacy in treating pancreatic cancer. (See Pet. at 7-9, 17-18, 21-22; Ex.

1210, 275:11-276:9, 280:12-283:15 (admitting claimed doses used or proposed in combination therapies).) *See Nalpropion Pharms., Inc. v. Actavis Lab'ys FL, Inc.*, 934 F.3d 1344, 1354-56 (Fed. Cir. 2019) (finding reasonable expectation of success when both drugs in combination treatment were known to affect the endpoint and combination and dose ranges taught or suggested in art). Further, because the claimed doses were in known ranges of use and the doses had all been used or proposed, a POSA had a reasonable expectation of success in arriving at the claimed invention.

Moreover, Petitioner's reasonable expectation of success is not based on an erroneous claim construction of "treating." (POR, 45-46.) The Board recognized a reasonable expectation of success when "treating" is construed to mean "more than a *de minimis* therapeutic benefit or efficacy for the patient being treated." (Paper 13 at 14, 37-39.). As highlighted by the Board, the asserted art showed proven therapeutic benefit for treatment with pancreatic cancer, including Conroy and Mahaseth's reference to FOLFIRINOX and Saif and Ko's reference to the clinical trial results of MM-398, as described in Bayever. (*Id.*, 37-39 (citations omitted).)

Finally, any reliance on general unpredictability in oncology is insufficient to overcome the strong case of obviousness here. A finding of "obviousness cannot be avoided simply by a showing of some degree of unpredictability in the art." *Pfizer*,

480 F.3d at 1364; *see also ImmunoGen, Inc. v. Vidal*, 653 F. Supp. 3d 258, 298–300 (E.D. Va. 2023), (finding reasonable probability of success and optimizing a result-effective variable within a disclosed range, even with evidence of unpredictability and without trials), *aff’d sub nom. ImmunoGen, Inc. v. Stewart*, 130 F.4th 1328, 1336 (Fed. Cir. 2025) (finite dosing options and prior-art parameters supply “direction as to which of many possible choices is likely to be successful”). Here, the art provided parameters for a POSA to start looking and there is no evidence the art taught away from the claimed doses. (*See* Sections II.B.1-2.)

3. The Dependent Claims Are Obvious.

Ipsen does not provide any arguments regarding the non-obviousness of claims 3-6 or 8-14, (*see generally* POR), and its arguments regarding claims 2, 7, and 15—made only in response to Ground 2 (POR at 53-57)—also fail.

Regarding administration order (Claims 2, 7, 15), the art taught administering liposomal irinotecan first and suggested subsequent administration of oxaliplatin, leucovorin, and then 5-FU. (*See* Ex. 1012, 3, 5 (disclosing said administration order); Ex. 1016, 1; Ex. 1006, 13-14, 33, claim 4.) POSAs would have considered sequencing and suggestions from other cancers. (Pet., 58-59; Ex. 1002, ¶¶308-309 (same); Ex. 1210, 236:12-237:9 (treatment information may be gleaned from other cancers).)

As to two-hour spacing interval (Claim 2), it was known that some reactions to oxaliplatin occur immediately upon administration and the infusion line needs to be flushed between drugs. (See Ex. 1038 at 2, 4.) A spacing interval to mitigate acute overlapping toxicities and line-compatibility constraints was logical, and there is no evidence of criticality for the claimed interval, confirming its obvious design choice.

Finally, regarding further administering a corticosteroid and an anti-emetic, Bayever discloses administering dexamethasone, a corticosteroid, and an anti-emetic to the patient prior to the antineoplastic therapy. (See Pet., 60; Ex. 1002, ¶¶310-11; Ex. 1006, 4-6, 33-35, claims 9, 18).)

C. No Impermissible Hindsight Was Employed.

“Practically speaking, and in terms of a long history of legal precedent, hindsight is not simply a chicken and egg scenario based on which action comes first.” *Am. Nat’l Mfg., Inc. v. Sleep Number Corp.*, IPR2019-00500, Paper 114 at 44-45 (PTAB Sept. 30, 2020) (citing and quoting *In re McLaughlin*, 443 F.2d 1392, 1395 (C.C.P.A. 1971) (“Any judgment on obviousness is in a sense ***necessarily a reconstruction based upon hindsight reasoning***, but so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made and does not include knowledge gleaned only from applicant’s disclosure, such a reconstruction is proper.”) (emphasis added).

Contrary to Ipsen’s suggestion, (POR 24-25), Ratain did not engage in impermissible hindsight and Ipsen has not shown he relied on information that could have been gleaned **only** from the disclosures of the patents at issue. *See Prolenium US Inc. v. Allergan Industrie, SAS*, IPR2020-00902, 2020 WL 7251424, at *27 (PTAB Dec. 9, 2020); *Shanghai Hongene Biotech Corp. v. Chemgenes Corp.*, IPR2023-00490, 2024 WL 3465176, at *27 (PTAB July 18, 2024). The asserted grounds and Ratain’s opinions start with the closest prior art, Conroy, and evaluate contemporaneous sources that provide clear reasons to modify it. *See supra* Section II.B.; *LKQ Corp. v. GM Glob. Tech. Operations LLC*, 102 F.4th 1280, 1298 (Fed. Cir. 2024) (holding that identifying a primary reference “protects against hindsight” and the “primary reference will likely be the closest prior art” most similar to the claims).

That Ratain testified that FOLFIRINOX was substantially similar to the Challenged Claims was not impermissible hindsight, but rather the POSA’s recognition that the prior art matched the claims. *See Micron Tech., Inc. v. Yangtze Memory Techs.*, IPR2024-0078, 2026 WL 30880, *20 (PTAB Jan. 5, 2026) (in rejecting PO’s hindsight argument and holding claims obvious, “Petitioner has referred to the [patent’s] claims, not its disclosure, to guide its assertions”); *Samsung Elecs. Co., Ltd. v. Netlist, Inc.*, IPR2022-00062, 2023 WL 5110321, *14 (PTAB May

8, 2023) (“We agree with Petitioner that Patent Owner’s assertion takes Petitioner’s expert’s testimony out of context, and that [Petitioner’s expert] made the combination from the point of view of a [POSA], and then considered whether the combination satisfied the claim language.”).

Moreover, FOLFIRINOX’s discussion in the Background of the ’552 patent—which was a known standard, shown by Conroy, Mahaseth, etc.—does not change the analysis. As recognized by the Board, “the fact that the inventor made the claimed invention for the same reason motivated by the prior art is evidence *that the invention was obvious, not that the Petitioner relied on hindsight-bias.*” *Samsung Elecs. Co., Ltd. v. Huawei Techs. Co., Ltd.*, IPR2017-01487, 2018 WL 6519544, *16 (PTAB Dec. 10, 2018) (emphasis added).

D. No Unexpected Results.

Ipsen’s claim of unexpected results is without merit. (*See* POR, 50-53.) Ipsen has not and cannot establish the requisite nexus or that the results were unexpected. Rather, the weight of evidence demonstrates there were no unexpected results.

1. Ipsen Fails to Establish a Nexus.

Neither Ipsen nor Oberstein offer any arguments or opinions regarding a nexus between the alleged unexpected results and the specific claimed method. (*See generally* POR; Ex. 1210, 380:5-17 (admitting no nexus opinion).) This alone should

be dispositive. Regardless, evidence of secondary considerations should only be considered after the proponent establishes a tie between the secondary considerations evidence and “the novel elements of the claim[s] at issue.” *Institut Pasteur v. Focarino*, 738 F.3d 1337, 1347 (Fed. Cir. 2013); *In re Huai-Hong Kao*, 639 F.3d 1057, 1068 (Fed. Cir. 2011).

Here, no nexus exists. Under any construction, the claims require specific doses of four drugs two weeks apart. (*See* Ex. 1001, 46:64-48:42). The NAPOLI-3 clinical study—relied upon to show unexpected results, (POR, 6, 51-53 (citing Ex. 2076, ¶¶66-68, 303-310)—does not and cannot establish any benefit from practicing these claims. There is no evidence that study participants, especially those who benefited, were given the claimed doses on the claimed schedule.

Indeed, most participants and even more of the long-term survivors experienced dose reductions and delays. (Ex. 1202 (52.5% and 60% of participants—and 66.7% and 80% of long-term survivors—received dose reductions of liposomal irinotecan and oxaliplatin, respectively; 70%-86.7% of participants received dose delays of same); Ex. 1207, 1 (same); Ex. 1201 (same).) Oberstein agrees and even admits that the evidence does not show what dosing patients actually received or at what cadence. (Ex. 1210, 374:19375:8, 377:19-379:11.)

In addition to receiving reduced doses and dose delays, patients who did the best were expected to do better. The long-term survivors were younger, fitter, and had lower cancer antigens. (*See* Ex. 1211, 3:01–3:34 (panelist explaining longer survival from this cohort would be “expected”); Ex. 1213, 2; Ex. 1210, 371:3–373:13 (agreeing the younger, fitter, patients with lower antigens received dose reductions and seem to have long-term survival).)

Therefore, any results from the NAPOLI-3 study cannot be shown to be the result of consistent dosing of the claimed doses. Accordingly, Ipsen cannot show a nexus to any alleged unexpected results.

2. Ipsen Has Not and Cannot Show Any Results Were Unexpected.

Ipsen’s specious claims of unexpected results—relying entirely on Oberstein’s testimony and arguing the results were a difference in kind, not just in degree—must also be rejected. (POR at 50-53 (relying exclusively on Oberstein’s opinions).) To assert unexpected results, “the patent owner must first show ‘what properties were expected.’” *Aventis Pharma S.A. v. Hospira, Inc.*, 743 F. Supp. 2d 305, 348 (D. Del. 2010); *see also Pfizer*, 480 F.3d at 1371. An evaluation of the significance and kind of results is also required. *Bristol-Myers Squibb Co. v. Teva Pharms. USA, Inc.*, 752 F.3d 967, 977 (Fed. Cir. 2014) (noting “‘differences in degree’ of a known and

expected property are not as persuasive in rebutting obviousness as differences in ‘kind’—i.e., a new property *dissimilar to the known property*”) (emphasis added).

As an initial matter, Oberstein confuses difference in kind versus degree, (Ex. 1210, 345:11-347:15), and the conclusory evidence Oberstein cites is not explained or cited in the response, (*see* POR, 50-53); this is not only insufficient but constitutes improper incorporation by reference. *See* 37 C.F.R. § 42.6(a)(3).

Ipsen has not shown what was expected or why the results were unexpected. It is undisputed that the claimed drugs and doses were all known and used to treat pancreatic cancer in combination regimens. (*See* Pet., 7-9, 17-18, 21-22; Ex. 2010, 275:11-276:9, 280:12-283:15 (admitting claimed doses used or proposed in combination therapies); *see also supra* Section II.B.1 (explaining doses disclosed in art). It is also undisputed that a POSA would expect dose reductions—which were commonly employed—to result in reduced toxicity. (*See* Ex. 2076, ¶308; Ex. 1002, ¶¶77-82.)

Contrary to any conclusory assertions otherwise, a POSA would expect comparable dose reductions to result in similar efficacy. (*See, e.g.*, Ex. 2076, Appendix B (compiling multiple references finding comparable dose reductions to result in comparable efficacy to FOLFIRINOX and reduced toxicity); Ex. 1216; Ex. 1002, ¶¶91, 149, 156 (providing examples).) Therefore, Ipsen’s assertion that any

alleged improvement was not an ‘expected, incremental change’ is unsupported. *See In re Sebelo Pat. Litig.*, No. 14-cv-06414, 2017 WL 3449054, at *27 (D.N.J. Aug. 11, 2017) (rejecting similar arguments and holding reduced side effects at lower doses is not unexpected).

Ipsen’s reliance on *Allergan, Inc. v. Sandoz Inc.*, is misplaced, (*see* POR 50-51), as the prior art there taught away from the claimed formula, which exhibited unexpected results. 796 F.3d 1293, 1306-07 (Fed. Cir. 2015). Here, neither Ipsen nor Oberstein point to any art teaching away from these dosages. (*See generally* POR, Ex. 2076.)

3. Post-Filing References Demonstrate a Lack of Unexpected Results.

Post-filing evidence confirms no unexpected benefit nor “fundamental therapeutic advance.” (POR 50-53.) As an initial matter, Ipsen does not dispute that (1) it did not disclose Wainberg’s cautions against comparison during prosecution, or (2) that the Examiner did not appreciate Wainberg’s clear limitations. (*Compare* Pet. at 34 *with generally* POR.); *see Apotex Inc. v. Cellgene Corp.*, IPR2023-00512, Paper 7 at 51-52 (PTAB Jul. 20, 2023) (finding error on unexpected results argument where Examiner did not cite reference and thus likely overlooked or misapprehended teachings).

Indeed, subsequent references refute any claim of NALIRIFOX's superiority. Nichetti found "no difference observed" in overall survival between NALIRIFOX and FOLFIRINOX, and Nevala-Plagemann concluded any difference was "not clinically [or] statistically significant," labeling NALIRIFOX a source of "financial toxicities." (*See* Pet. 34-35, 51-52; Ex. 1002, ¶¶258-262 (citing Ex. 1010 at 1, 5; Ex. 1011 at 1-2).) Nichetti also observed a lower overall survival in NALIRIFOX (11.1 months) vs FOLFIRINOX (11.7 months). (*See* Ex. 1002, ¶258 (citing Ex. 1010 at 1, 5).) Even Skorupan, a reference previously cited by Ipsen (Paper 9 at 50-51), concedes that the relative efficacy of NALIRIFOX versus FOLFIRINOX "has yet to be explored" and that NALIRIFOX is "more costly." (Ex. 2033, 1, 3.)

Ipsen's data does not suggest NALIRIFOX had better efficacy for long-term survival. (*See* Ex. 1200 ¶7 (citing Ex. 1203 and noting a greater percentage of FOLFIRINOX patients experienced long-term survival); Ex. 2031 (Ipsen Poster admitting comparison between NALIRIFOX and FOLFIRINOX "has not been studied"); Ex. 2032 (admitting direct comparison between the NAPOLI-3 results and FOLFIRINOX are "not possible"); *supra* Sections II.D.1-2.)

The 2025 NCCN Guidelines (the industry’s “recognized standard”⁴) reflect this consensus by identifying FOLFIRINOX as the top preferred treatment (followed by Gem+NabP) and stating that NALIRIFOX “does not appear to have an advantage over FOLFIRINOX and adds considerably more expense,” despite multiple submissions from Ipsen requesting to hold otherwise. (Ex. 1206 at 45-55, 87; Exs. 1218-1221 (Ipsen requesting changes to guidelines and NCCN holding steadfast to statements regarding NALIRIFOX’s lack of advantage and considerable expense compared to FOLFIRINOX).)

While raised only through improper incorporation by reference, the ICER (“incremental cost effectiveness ratio”)—a measurement of the value for cost—for NALIRIFOX is between \$1.37M and \$1.95M. (*See* Ex. 1217 (finding a “0%” probability of cost-effectiveness and that NALIRIFOX “far exceeds currently acceptable thresholds for economic value”); Ex. 2029 (similarly finding NALIRIFOX “outside of any conventional boundary of acceptable value threshold”).

⁴ National Comprehensive Cancer Network, *About Clinical Practice Guidelines* <https://www.nccn.org/guidelines/guidelines-process/about-nccn-clinical-practice-guidelines> (last visited Feb. 10, 2026).

III. CONCLUSION

Petitioners respectfully request that the Board find claims 1–15 of the '552 patent unpatentable and cancel the claims.

Dated: February 11, 2026

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CERTIFICATE OF COMPLIANCE

Pursuant to 37 C.F.R. § 42.24(d), the undersigned certifies that the foregoing Petitioners' Reply to Patent Owner's Response contains, as measured by the word-processing system used to prepare this paper, 5,583 words. This word count does not include the items excluded by 37 C.F.R. § 42.24 as not counting towards the word limit.

Dated: February 11, 2026

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CERTIFICATE OF SERVICE

Pursuant to 37 CFR § 42.6(e), the undersigned hereby certifies that on February 11, 2026, the foregoing Petitioners' Reply to Patent Owner's Response and supporting exhibits were served via electronic mail, as authorized by Patent Owner, at the following email addresses:

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