

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

APOTEX, INC.,
Petitioner,

v.

IPSEN BIOPHARM LTD.,
Patent Owner.

Case No. IPR2025-01531
U.S. Patent No. 11,344,552

PATENT OWNER'S PRELIMINARY RESPONSE

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Ex. 2007	Deposition Transcript of Mark J. Ratain In the Matter of CSPC Pharma vs. Ipsen Biopharm, dated October 24, 2025 (“Ratain Deposition”)
Ex. 2015	Maria Syl D. De La Cruz, et al., <i>Diagnosis and Management of Pancreatic Cancer</i> , Am Fam Physician, 89(8):626-632 (2014) (“De La Cruz”)
Ex. 2016	Marvin Schober, et al., <i>New Advances in the Treatment of Metastatic Pancreatic Cancer</i> , Digestion, 92(3):175-184 (2015) (“Schober”)
Ex. 2017	Maria L. Rossi et al., <i>Therapeutic options for the management of pancreatic cancer</i> , 20(32) World J. Gastroenterol. 11142 (2014) (“Rossi”)
Ex. 2018	File History of U.S. Patent No. 11,344,552, Feb. 25, 2022 Remarks (“February 25, 2022 Remarks”)
Ex. 2019	Dorland’s Illustrated Medical Dictionary (32nd ed. 2012) (“Dorland’s Dictionary”)
Ex. 2020	Stedman’s Medical Dictionary for the Health Professions and Nursing (7th ed. 2012) (“Stedman’s Dictionary”)
Ex. 2021	Taber’s Cyclopedic Medical Dictionary (22nd ed. 2013) (“Taber’s Dictionary”)
Ex. 2011	Robert De W. Marsh et al., <i>Pancreatic cancer and FOLFIRINOX: a new era and new questions</i> , Cancer Med. 2015 Jun;4(6):853-63 (2015) (“Marsh”)
Ex. 2022	Original French language publication of Supplemental Protocol to: Thierry Conroy et al., <i>FOLFIRINOX versus Gemcitabine for Metastatic Pancreatic Cancer</i> , N. Engl. J. Med., 364(19):1817-25 (2011), available at https://www.nejm.org/doi/full/10.1056/NEJMoa1011923 (“Original Conroy Protocol”)
Ex. 2023	Matias E. Valsecchi et al., <i>Recent Treatment Advances and Novel Therapies in Pancreas Cancer: A Review</i> , 45 J. Gastrointest. Cancer 190 (2014) (“Valsecchi”)
Ex. 2024	Samir D. Undevia, et al., <i>Pharmacokinetic Variability of Anticancer Agents</i> , Nat Rev Cancer, 5(6):447-458 (2005) (“Undevia”)
Ex. 2025	U.S. Patent No. 7,807,350 to Ratain et al. (“the ’350 patent”)

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Ex. 2026	Mark J. Ratain, et al., <i>Dose-finding and Pharmacokinetic Study to Optimize the Dosing of Irinotecan According to the UGT1A1 Genotype of Patients with Cancer</i> , J Clin Oncol., 32(22):2328-2334 (2014) (“Ratain 2014”)
Ex. 2027	Dylan M. Bach, et al., <i>Therapeutic drug monitoring in cancer chemotherapy</i> , Bioanalysis. 2010 May;2(5):863-79 (“Bach”)
Ex. 2028	H Gurney, et al., <i>How to calculate the dose of chemotherapy</i> , Br J Cancer 86, 1297–1302 (2002) (“Gurney”)
Ex. 2029	Alnaim, <i>Therapeutic Drug Monitoring of Cancer Chemotherapy</i> , J Oncol Pharm Pract., 13(4):207-221 (2007) (“Alnaim”)
Ex. 2030	Biotechnology Innovation Organization et al., <i>Clinical Development Success Rates 2006-2015</i> (2016) (“BIO study”)
Ex. 2031	Ramya Thota et al., <i>Preclinical Rationale for the Phase III Trials in Metastatic Pancreatic Cancer: Is Wishful Thinking Clouding Successful Drug Development for Pancreatic Cancer?</i> , 46(2) Pancreas 143 (2017) (“Thota”)
Ex. 2032	Mark J. Ratain, <i>Phase II Oncology Trials: Let’s Be Positive</i> , 11(16) Clin. Cancer Rsch. 5561 (2005) (“Ratain 2005”)
Ex. 2033	Xiayu Jiao, et al., <i>Comparative effectiveness of NALIFIROX vs. FOLFORINOX in pancreatic cancer</i> , JCO 42, 4160-4160(2024) (“Jiao”)
Ex. 2034	Zuojuan Xiang et al., <i>Cost-effectiveness analysis of first-line combination chemotherapy regimens for metastatic pancreatic cancer and evidence-based pricing strategy of liposomal irinotecan in China</i> . Front Pharmacol. 2024 Dec 20;15:1488645 (“Xiang”)
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Ex. 2013	Nebojsa Skorupan et al., <i>First-Line Treatment of Metastatic Pancreatic Ductal Adenocarcinoma: Did 2024 Offer New</i>

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	<i>Insights?</i> , ASCO Daily News, available at https://dailynews.ascopubs.org/do/first-line-treatment-metastatic-pancreatic-ductal-adenocarcinoma-did-2024-offer-new (“Skorupan”)
Ex. 2037	S. Kobayashi, et al., <i>1527P GnP vs mFOLFIRINOX or S-IROX in metastatic pancreatic cancer: 1-year follow-up updated data from the GENERATE (JCOG1611)</i> , Annals of Oncology, Volume 35, S932 (2024) (“Kobayashi”)
Ex. 2038	Jennifer J. Knox et al., <i>Early results of the PASS-01 trial: Pancreatic adenocarcinoma signature stratification for treatment-01</i> , JCO 42, LBA4004-LBA4004 (2024) (“Knox”)

I. INTRODUCTION

Patent Owner Ipsen Biopharm Ltd. (“Ipsen”) files this Patent Owner’s Preliminary Response to the petition filed by Apotex, Inc. (“Apotex”). A Notice of Filing Date Accorded was entered on September 23, 2025. Paper 4. As set forth below, Apotex fails to show a reasonable likelihood that it will prevail in showing that any challenged claim of U.S. Patent No. 11,344,552 (“the ’552 patent”) is obvious.

At the outset, the Board should deny institution under 35 U.S.C. § 325(d) because Apotex relies on the same prior art and arguments already considered and overcome by the Patent Office. The Director’s finding, in the CSPC IPR¹, that the prior art discloses critical claim limitations is incorrect—the references unambiguously teach a different treatment regimen than what Apotex contends, with the dosage Apotex relies upon disclosed only in the limited context of post-treatment dose adjustments for patients experiencing adverse events. The Examiner properly evaluated the prior art based on its primary teachings, and Apotex has failed to show the Patent Office materially erred in its assessment.

To the extent that Apotex purports to present new arguments in its petition, those arguments are rooted in improper hindsight and, thus, fail. Indeed, Apotex

¹ IPR 2025-00505. CSPC is defined for purposes herein to be CSPC Pharmaceutical Group Limited, CSPC Ouyi Pharmaceutical Co., Ltd., and Conjupro Biotherapeutics, Inc.

begins its obviousness challenge with FOLFIRINOX, which it repeatedly describes as the “gold standard” of care in the relevant field, and allegedly obvious modifications thereto. But this starting point itself reveals the hindsight-driven nature of Apotex’s challenge: its expert, Dr. Ratain² testified that he began his analysis with FOLFIRINOX based on its “similarity” to the ’552 patent claims—in other words, working backward from the claimed invention. Ex. 2007 at 29:4-20; 35:12-36:5; 39:24-41:16. Dr. Ratain further admitted that his review of the ’552 patent’s specification and claim elements drove his selection of other asserted references, confirming that the patent itself guided his obviousness analysis. *Id.* Even assuming a person of ordinary skill in the art at the time of the invention (“POSA”) would have been motivated to start with and then depart from the “gold standard” treatment (one would not), Apotex fails to establish why a POSA would

² Apotex submitted a declaration of its own expert, Dr. Dreicer, along with its Petition. *See* Ex. 1501. In its Motion for Joinder to the CSPC IPR, Apotex stated “If CSPC allows, Apotex will rely on CSPC’s declarant and withdraw its own declarant. Even if CSPC does not allow that, if CSPC’s expert’s declaration and deposition transcript become publicly available, Apotex will rely on the publicly available declaration and transcript and withdraw its own declaration.” Paper 3 at 5. Counsel for Apotex stated in correspondence dated November 24, 2025 that “[i]n view of the transcript of CSPC’s expert, Dr. Ratain, becoming available in IPR2025-00505 earlier this month, we will withdraw the declaration of our expert, Dr. Dreicer.” Therefore, arguments herein are directed to Dr. Ratain’s opinions, rather than Dr. Dreicer’s. In any event, as Apotex stated “Apotex’s expert declaration is substantially identical to CSPC’s expert declaration.” Paper 3 at 5.

have made the specific, simultaneous modifications necessary to arrive at the claimed invention. Apotex's approach is piecemeal, addressing each modification independently rather than explaining why a POSA would combine them all at once—a telltale sign of improper hindsight reasoning.

Moreover, Apotex ignores that the prior art disclosed numerous alternative approaches for addressing the only motivating factor Apotex identifies. As discussed herein, Apotex's own references teach that these prior-art methods—none of which lead to the claimed invention—adequately addressed Apotex's purported motivating factor without requiring the extreme measure of the modifications Apotex now claims were obvious, including substitution with an entirely new active ingredient. Apotex also ignores the low likelihood of success in the field, which would have further discouraged a POSA from pursuing the claimed modifications. Indeed, pancreatic cancer has the highest Phase III failure rate of all cancers at 87% and the lowest Phase III success rate in oncology. Apotex's reliance on preclinical and early-stage clinical data to establish reasonable expectation of success at arriving at the claimed invention via its distinct, simultaneous modifications is unavailing, as Apotex's expert's own publications acknowledge that such data does not predict clinical trial success. For at least these reasons, the Board should decline to institute proceedings.

Ultimately, as discussed herein, each of Petitioner’s Grounds contains a fatal flaw and institution of *inter partes* review of the ’552 patent should be denied.

II. BACKGROUND

Pancreatic cancer is one of the leading causes of cancer-related deaths in the U.S. and, due to lack of early clinical symptoms, is usually diagnosed at a late or otherwise advanced stage. Metastatic pancreatic cancer is the most advanced stage of the disease, and it is notoriously difficult to treat, with a grim prognosis and limited therapeutic options. In patients diagnosed with metastatic pancreatic cancer, the median overall survival is less than one year, and the five-year survival rate is approximately 2%.

Treatment goals for advanced-stage or metastatic pancreatic cancer are palliation and improved survival. *See* Ex. 2015 (De La Cruz) at 5. As of 2015, available treatment options aimed to increase overall survival in first-line patients. *See, e.g., id.* (noting that, for first-line patients, “the most recent phase III trials improve survival by only several months”); Ex. 2016 (Schober) at 2 (“Despite numerous clinical trials in stage IV metastatic PDAC, there has only been a modest improvement of median survival rates.”). As of 2015, treatment options for patients with advanced or metastatic pancreatic cancer included chemotherapy, radiation therapy, and personalized therapy. *See* Ex. 2017 (Rossi) at 5.

Chemotherapy treatment for metastatic pancreatic cancer has evolved over the years, as different chemotherapy drugs became available for use alone or in combination with other chemotherapy drugs.

Gemcitabine is an antimetabolite drug that has been used in the treatment of metastatic pancreatic cancer, alone or in combination with other chemotherapy drugs, since the 1990s. *See* Ex. 1047 at 1. In 1997, gemcitabine became the first-line choice for treatment of pancreatic cancer, owing to relatively fewer side effects than existing options as well as a survival benefit. Ex. 2016 (Schober) at 3. As of 2015, gemcitabine was used in combination with other classes of drugs in the treatment of metastatic pancreatic cancer. *See id.* at 4-5.

In 2011, FOLFIRINOX became a preferred first-line treatment option for patients with metastatic pancreatic cancer, following clinical study results that showed an improvement in overall survival (11.1 months vs. 6.8 months) over gemcitabine. *See* Ex. 1003 (Conroy) at 1. FOLFIRINOX is a chemotherapy regimen that is a combination four different chemotherapy drugs at different starting doses: 85 mg/m² oxaliplatin, 180 mg/m² irinotecan, 400 mg/m² leucovorin, and 400 mg/m² bolus of 5-fluorouracil, followed by a 2400 mg/m² continuous infusion of 5-fluorouracil. *Id.* at 3. After FOLFIRINOX emerged as a preferred first-line treatment option, variations on the dosage(s) of its constituent components were used

in order to address toxicity issues with the multi-drug chemotherapy treatment regimen.

III. THE '552 PATENT

Ipsen's Onivyde[®] (irinotecan liposome injection) is a treatment for metastatic pancreatic cancer. The FDA recently approved Onivyde[®] as a first-line treatment for adult patients with metastatic pancreatic adenocarcinoma. Onivyde[®]'s first-line treatment regimen, referred to as "NALIRIFOX," is a combination therapy consisting of four different chemotherapy drugs, administered in specific doses and frequency.

The '552 patent recites methods of treatment in accordance with Onivyde[®]'s first-line treatment regimen, NALIRIFOX. Claim 1 is representative:

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/m² of liposomal irinotecan,
- b. 60 mg/m² oxaliplatin,
- c. 200 mg/m² of the (l)-form of leucovorin or 400 mg/m² of the (l+d) racemic form of leucovorin, and
- d. 2,400 mg/m² 5-fluorouracil;

to treat the metastatic adenocarcinoma of the pancreas in the human patient.

Ex. 1001 ('552 patent), claim 1. Claim 12, the other independent claim, recites the same combination therapy for a patient “who has not previously received gemcitabine.” *Id.* at claim 12. Dependent claims 2-11 and 13-15 recite specific sequences for administration of the claimed combination therapy and other formulation details. *Id.* at claims 2-11, 13-15.

The '552 patent issued on May 31, 2022, after overcoming the same type of obviousness arguments that Apotex reiterates in its petition. As discussed in Ipsen's discretionary denial brief, (*see* Paper 9 at 7-8), the '552 patent applicant overcame obviousness rejections that were based on Conroy (Ex. 1003) and Bayever (Ex. 1006), the same two lead references that Apotex now relies upon here. *See* Ex. 1084 at 190-201 (Mar. 6, 2018 Rejection); *id.* at 314-327 (Sept. 11, 2018 Rejection); Ex. 1088 at 57-69 (July 8, 2019 Rejection); Ex. 1097 at 188-203 (Feb. 27, 2020 Rejection); Ex. 1119 at 9-22 (Aug. 26, 2021 Rejection). Thus, the Patent Office has already decided the issue of obviousness based on those two references in Ipsen's favor.

IV. PERSON OF ORDINARY SKILL IN THE ART

Apotex and its expert Dr. Ratain argue that a 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, pharmaceuticals, 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.” Paper 1 at 26. Further, Apotex and Dr. Ratain argue that a POSA “would have been part of a team of professionals with these credentials and post-doctoral experience.” *Id.*

Ipsen disagrees with Apotex’s and Dr. Ratain’s definition of a POSA but assumes their definition for purposes of the arguments presented herein. As discussed below, under this definition of a POSA, Apotex fails to show a reasonable likelihood of success in prevailing in its obviousness challenge of any of the challenged claims.

V. CLAIM CONSTRUCTION

In an *inter partes* review, the Board applies 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 that standard, claim terms “are generally given their ordinary and customary meaning” as understood by a POSA. *Phillips v. AWH Corp.*, 415 F.3d 1303, 1312-13 (Fed. Cir. 2005) (en banc) (quoting *Vitronics Corp. v. Conceptronic, Inc.*, 90 F.3d 1576, 1582 (Fed. Cir. 1996)). Claim terms need only be construed if they are in controversy, and only to the extent necessary to resolve the controversy. *See Vivid Techs., Inc. v. Am. Sci. & Eng’g, Inc.*, 200 F.3d 795, 803 (Fed. Cir. 1999).

A. The Proper Construction of “Treat” / “Treating” is Its Plain and Ordinary Meaning

The ’552 patent’s claimed methods of treatment should be understood to have their plain and ordinary meaning, as a POSA would understand them in light of the claims, specification, and prosecution history. The ’552 patent claims recite, *inter alia*, “method[s] of treating metastatic adenocarcinoma of the pancreas in a human patient” comprising “administering an antineoplastic therapy” that consists of the recited drugs, in recited dosages, in accordance with a recited schedule. *See* Ex. 1001 at claim 1. The specification provides examples of the claimed methods of treatment, including their effects in the recited patient population. *See, e.g.*, Ex. 1001 at 21:30-43:19 (Example 3, “Treatment of Pancreatic Cancer”), 43:21-46:16 (Example 4, “Tolerability of Antineoplastic Therapies in Human Clinical Trial”). During prosecution, the ’552 patent applicant cited evidence of the claimed methods’ unexpected results, in the form of clinical effects such as prolonged or progression-free survival, safety, and tolerability. *See, e.g.*, Ex. 2018 (February 25, 2022 Remarks); Ex. 1119 at 151-54.

Based on all of this, a POSA would understand that “treatment” has its plain and ordinary meaning, for example, “the management and care of a patient for the purpose of combating disease or disorder.” Ex. 2019 (Dorland’s Dictionary) at 3; *see also* Ex. 2020 (Stedman’s Dictionary) at 3 (“Medical or surgical management of a patient.”); Ex. 2021 (Taber’s Dictionary) at 3 (“1. Medical, surgical, dental, or

psychiatric management of a patient. 2. Any specific procedure used for the cure or the amelioration of a disease or pathological condition.”). “Treatment,” as used in the ’552 patent, refers to management and/or care comprising antineoplastic therapy in accordance with the claims and specification. This is consistent with Dr. Ratain’s testimony. *See* Ex. 2007 at 91:16-23 (defining “effective” as “to treat one or more symptoms of the disease and/or to reduce the size of the tumor or reduce the rate of growth of the tumor.”).

The management and care for the purpose of combating a disease is accomplished for the claimed treatment methods, according to the ’552 patent, using certain doses that are effective. *See, e.g.,* Ex. 1001 at 9:57-10:54 (regarding a “therapeutic use of liposomal irinotecan”), 18:32-41 (regarding a “therapeutically effective” dose of liposomal irinotecan), 12:6-11 (regarding an “effective” dose of fluorouracil), 12:35-45 (regarding an “effective” dose of leucovorin), 12:53-58 (regarding an “effective” dose of oxaliplatin). Thus, the claims cover effective methods of treatment. And Apotex’s proposed construction, which does not require actual efficacy, is at odds with the plain and ordinary meaning of “treat” and “treatment.”

B. Apotex’s First Proposed Construction of “Treat” / “Treating”

Apotex argues claim construction on alternative grounds. For Grounds 1 and 2, Apotex argues that “treating” and “treat” should be understood to mean

“attempting to cause a therapeutic improvement but not requiring actual efficacy.”
See Paper 1 at 29-33. Under this construction, Apotex argues that the ’552 patent’s effective filing date is August 21, 2015. *Id.* at 39.

The verbiage of Apotex’s proposed construction finds no support anywhere in the ’552 patent specification. The proper construction of those terms is that which a POSA would understand them to have, read in the context of the surrounding claim language and specification. *See Phillips*, 415 F.3d at 1313. As the Federal Circuit has stated, a patent’s specification “is always highly relevant to the claim construction analysis,” and it is “the single best guide to the meaning of a term.” *Id.* at 1315 (quoting *Vitronics*, 90 F.3d at 1582 (internal quotations omitted)). Nowhere in the specification does the phrase “attempting to cause a therapeutic improvement but not requiring actual efficacy” appear. Thus, there is no basis in the ’552 patent specification for Apotex’s proposed construction.

The Board should moreover reject Apotex’s proposed construction, because it conflicts with the ’552 patent specification’s description of the invention. A construction that is inconsistent with the specification’s description of the invention should be rejected. *See, e.g., Apple Inc. v. Masimo Corp.*, No. 2022-1890, 2024 WL 137336, at *3 (Fed. Cir. Jan. 12, 2024) (affirming the Board’s rejection of a claim construction that “improperly takes the term out of context of the patented invention and lacks support.”). As discussed *supra*, the ’552 patent specification teaches that

the claimed doses are “effective.” *See, e.g.*, Ex. 1001 at 9:57-10:54, 18:32-41, 12:6-11, 12:35-45, 12:53-58. Apotex’s construction, “attempting to cause a therapeutic improvement but not requiring actual efficacy,” is inconsistent with the ’552 patent’s description of the invention. Apotex’s construction is therefore inconsistent with the ’552 patent’s specification and should be rejected as such.

To the extent that Apotex cites portions of the specification allegedly supporting its construction, those portions are not definitional. Apotex suggests that portions of the ’552 patent’s “Summary” define the claimed methods of treatment “solely by administration of the drugs and not by clinical efficacy.” *See* Paper 1 at 31 (citing Ex. 1001 at 2:26-46). The cited portions do not purport to define any claim term, let alone “treat” or “treatment.” *See* Ex. 1001 at 2:26-46.

Apotex’s other arguments ignore the intrinsic record. Apotex suggests that it was a deliberate choice by the ’552 patent applicant to avoid claim terms that imply any therapeutic effect. *See* Paper 1 at 31-32. In doing so, Apotex ignores that the claims recite methods of treatment that comprise an “antineoplastic therapy,” which the specification describes in terms of its constituent components and clinical effects. *See, e.g.*, Ex. 1001 at 11:61-67 (describing combination treatment that comprises liposomal irinotecan in combination with oxaliplatin, leucovorin, and 5-fluorouracil), 23:53-66 (Table 2, Level -1), 44:58-45:19.

Nor does Apotex provide any citation of the intrinsic record to support its assertion that the '552 patent applicant “*deliberately chose to delete* ‘therapeutically effective’ and ‘effective treatment’ from the claim language.” See Paper 1 at 32 (emphasis added). Instead, Apotex cites cases decided on different factual circumstances from those present here. Unlike in *Novartis*, the claims here recite specific drugs and dosages that the specification describes as providing therapeutic effect. See *Novartis Pharms. Corp. v. Actavis, Inc.*, No. 12-366, 2013 WL 6142747, at *10 (D. Del. Nov. 21, 2013); Ex. 1001 at 2:26-46; see also *id.* at 21:30-43:19 (Example 3); 43:20-46:16 (Example 4). Unlike in *Pfizer v. Teva*, there is no evidence that the '552 patent applicant “specifically deleted references in patented claims.” See *Pfizer Inc. v. Teva Pharms. USA, Inc.*, 803 F. Supp. 2d 397, 407 (E.D. Va. 2011). Apotex is incorrect to suggest that the intrinsic record here is analogous to that of the cases it cites.

Apotex identifies no credible extrinsic evidence in support of its proposed construction. Apotex cites no technical dictionary definitions. To the extent that Apotex relies on its expert Dr. Ratain, his testimony is either duplicative of Apotex's arguments or uninformed by the intrinsic record. Dr. Ratain, like Apotex, cites portions of the “Summary” section of the specification that are not definitional. Ex. 1002 at ¶¶ 52-54 (citing Ex. 1001 at 2:23-65). Dr. Ratain additionally relies on the '552 patent's discussion of animal studies to argue that the “Patent Owner used the

word ‘treatment’ synonymously with administration or exposure to.” Ex. 1002 at ¶ 55. Dr. Ratain ignores, however, that the cited passages refer to a study of a “mouse xenograft model,” whereas the claimed methods are for treating “metastatic adenocarcinoma of the pancreas in a human patient.” *Compare* Ex. 1001 at 8:31-36 *with* claim 1. Discussion of “treatment” in the context of an animal study is inapposite where, as here, the claimed “treatment” is specifically directed to a “human patient.”

C. Apotex’s Second Proposed Construction of “Treat” / “Treating”

For Ground 3, Apotex relies on an alternative, unspecified construction of “treat” and “treating” that would require “a showing of clinical efficacy.” Paper 1 at 39-41. Apotex otherwise fails to articulate what such a construction would entail. Under this alternative “construction,” Apotex argues that the effective filing date is no earlier than November 10, 2017. *Id.* at 39.

Apotex cites no support in the specification for its alternative “construction.” At most, Apotex suggests that the ’552 patent applicant’s arguments during prosecution compel a claim requirement of clinical efficacy. *See* Paper 1 at 38 (“[T]he Patent Owner argued that the Challenged Claims are *directed to clinical efficacy* in a human suffering from metastatic pancreatic cancer.” (citing Ex. 1119 at 153) (emphasis added)). The page that Apotex cites appears in the ’552 patent applicant’s February 25, 2022 remarks, under the heading, “Unexpected Results.”

See Ex. 1119 at 152-53. In this section, the '552 patent applicant does not argue—as Apotex alleges—that the claims are “directed to clinical efficacy,” but rather, as discussed *supra*, the '552 patent applicant argues that the claimed therapy has “unexpected therapeutic effects.” Ex. 1119 at 153.

VI. THE '552 PATENT CLAIMS HAVE AN EFFECTIVE FILING DATE OF AUGUST 21, 2015

The '552 patent has an effective filing date of August 21, 2015, which is the filing date of its earliest priority application, U.S. Provisional Application No. 62/208,209 (“the '209 application”). Apotex’s argument to the contrary relies on a claim-construction position that fails for the reasons discussed *supra*. As set forth below, the '209 application provides written-description support for the '552 patent’s claimed therapies.

The '209 application adequately describes the '552 patent’s claimed combination therapy. The written-description requirement is met where the disclosure “reasonably conveys to those skilled in the art that the inventor had possession of the claimed subject matter as of the filing date.” *Ariad Pharm., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1351 (Fed. Cir. 2010). The '209 application, the disclosure of which is incorporated by reference in the '552 patent specification (*see* Ex. 1001 at 1:9-17), describes combination therapies that include liposomal irinotecan, oxaliplatin, leucovorin, and 5-FU for the first-line treatment of metastatic pancreatic cancer. *See, e.g.*, Ex. 1015 at 6 ([0006]), 114 (claims 1, 3). As the '209

application describes, these combination therapies are for the treatment of metastatic pancreatic cancer, with clinical effects described by reference to outcome measures. *See, e.g., id.* at 22-25 ([00090]-[00107]). The '209 application moreover describes a regimen that includes each of the claimed drugs in the recited dosages, administered in accordance with the recited frequency. *See, e.g., id.* at 19 ([0075]), 20 ([0077]-[0080]), 63-64 ([0287]-[0288]), 114 (claims 4-12). In view of at least these disclosures, a POSA would understand the inventors to have been in possession of the claimed methods at the time of the '209 applications' filing.

It is sufficient, as the '209 application does, to describe the claimed therapy in enough detail such that a POSA would understand the inventors to have been in possession of the claimed therapy. Adequate written description does not require “either examples or an actual reduction to practice.” *Allergan, Inc. v. Sandoz Inc.*, 796 F.3d 1293, 1308 (Fed. Cir. 2015). The level of detail required in order to satisfy the requirement “varies depending on the nature and scope of the claims and on the complexity and predictability of the relevant technology.” *Ariad*, 598 F.3d at 1351. Moreover, “[a] claim that recites a property that is necessarily inherent in a formulation that is adequately described is not invalid as lacking written description merely because the property itself is not explicitly described.” *Allergan*, 796 F.3d at 1309. Here, the claims recite a specific combination of drugs, in specific doses, administered at a specific frequency. *See* Ex. 1001 at claim 1. The '209 application

discloses this specific treatment regimen. Ex. 1015 at 63-64 ([0287]-[0288]). The clinical effects of the claimed therapy were later affirmed in clinical trial publications. *See, e.g.*, Ex. 1018 at 9 (“No new safety signals were observed with first-line NALIRIFOX in patients with locally advanced or metastatic PDAC, and anti-tumour activity was promising.”); Ex. 1019 at 7-8 (“Results”). Thus, the ’209 application adequately describes the ’552 patent’s claimed combination therapy.

VII. INSTITUTION SHOULD BE DENIED UNDER § 325(D)

At the outset, the Board should deny institution under 35 U.S.C. § 325(d) because Apotex relies on identical or substantially the same prior art and arguments previously considered by the Patent Office, and fails to show that the Patent Office materially erred. As detailed in Ipsen’s request for discretionary denial of the CSPC petition (Paper 9 at 15-16), CSPC presented these same arguments based on the same lead references that the Patent Office already considered and decided in Ipsen’s favor. *See* Ex. 2002 at 8-18. Apotex makes identical arguments in its Petition. Paper 1 at 1.

A two-part analysis applies to the Board’s authority to deny institution under § 325(d). *Advanced Bionics, LLC v. Med-El Elektromedizinische Geräte GMBH*, IPR2019-01469, Paper 6 at 9-10 (precedential). First, the Board considers whether “the same or substantially the same” art or arguments were previously presented to the Patent Office. *Id.* at 8. If either is met, the Board then considers whether the

Petitioner demonstrates that the Patent Office “erred in a manner material to the patentability of the challenged claims.” *Id.* In applying the two-part framework, the Board considers several nonexclusive factors set forth in *Becton, Dickinson & Co. v. B. Braun Melsungen AG*, IPR2017-01586, Paper 8 at 17-18 (PTAB Dec. 15, 2017) (precedential as to § III.C.5, first paragraph).

The Director has already found by implication that CSPC (and Apotex, as “silent understudy”) presents the “the same or substantially the same art or arguments” that were previously presented to the Patent Office. In declining Ipsen’s request for discretionary denial of CSPC’s petition, the Director did not dispute that CSPC’s petition presents the same or substantially the same arguments the Patent Office already considered and decided in Ipsen’s favor. Ex. 2003 at 3. Rather, the Director bypassed the first step of the *Advanced Bionics* analysis, impliedly finding that step met by resting its decision on the second step—whether there has been a showing that the Patent Office erred in a manner material to patentability. *See id.*; *Advanced Bionics, LLC*, IPR2019-01469, Paper 6 at 7-8. The Director found that CSPC “provide[d] persuasive evidence that the Office erred in a manner material to the patentability of the challenged claims by not considering or overlooking specific teachings in Conroy’s appendix and Conroy’s associated protocol, both identified in Conroy itself, that disclose critical limitations in the claims.” Ex. 2003 at 3. As explained below, there was no such material error. At minimum, there can be no

dispute that CSPC and, thus, Apotex rely on the same or substantially the same art or arguments as already presented and overcome before the Patent Office. Therefore, Apotex's arguments under the first part of the *Advanced Bionics* analysis are unavailing.

The Director's finding that the Conroy Appendix and the Conroy Protocol "disclose critical limitations in the claims" is incorrect. Apotex argues that the Patent Office "never recognized that Conroy, the Conroy Protocol, and the Conroy Appendix disclose that FOLFIRINOX patients were administered with 60 mg/m² oxaliplatin." Paper 1 at 36. This fundamentally mischaracterizes what the Conroy references teach.

Conroy defines FOLFIRINOX as "oxaliplatin, 85 mg per square meter of body-surface area; irinotecan, 180 mg per square meter; leucovorin, 400 mg per square meter; and fluorouracil, 400 mg per square meter given as a bolus followed by 2400 mg per square meter given as a 46-hour continuous infusion, every 2 weeks." Ex. 1003 at 1; *see id.* at 3. The Conroy Protocol specifies that FOLFIRINOX treatment "will begin with oxaliplatin 85 mg/m² IV infused over 2 hours." Ex. 1004 at 15. Dr. Ratain, Apotex's expert, did not dispute that the Conroy Protocol teaches 85 mg/m² oxaliplatin as the starting dose. Ex. 2007 at 43:11-14, 83:11-18.

Subsequent references, including those co-authored by Conroy himself, confirm this understanding. Conroy 2013 states that “[t]he FOLFIRINOX regimen included oxaliplatin (85 mg/m²) over 2 h.” Ex. 1041 at 2-3. Other references refer to Conroy’s FOLFIRINOX regimen as comprising 85 mg/m² oxaliplatin. *See, e.g.*, Ex. 2011 (Marsh) at 1-2 (“Promising phase II results with FOLFIRINOX (FFX) (oxaliplatin 85 mg/m² . . .) were confirmed in a sentinel phase III study (PRODIGE 4/ACCORD 11”); *see also* Ex. 2007 at 85:8-13, 97:21-98:4 (Dr. Ratain agreeing that other papers’ reference to FOLFIRINOX refers to a regimen comprising 85 mg/m² oxaliplatin).

To the extent the Conroy references refer to doses of oxaliplatin lower than 85 mg/m², it is only in the limited context of dose adjustment for some patients following “predefined toxic events.” Ex. 1003 at 3; Ex. 1004 at 15-20; Ex. 1017 at 3-9. At most, the Conroy references teach that toxicity events may prompt dose reduction *after* treatment comprising 85 mg/m² oxaliplatin has initiated and only for some patients under certain circumstances.

This distinction is critical. The disclosure of 60 mg/m² as a **post-toxicity reduced dose** is entirely cumulative of Conroy’s primary teaching that FOLFIRINOX comprises 85 mg/m² oxaliplatin and that doses may be adjusted downward in response to toxicity. A POSA reading the Conroy Protocol and Appendix would understand that 60 mg/m² represents a responsive modification

after initiating treatment at the standard 85 mg/m² dose—not a suggested starting dose for a new treatment regimen. The Examiner properly evaluated Conroy based on its teaching of 85 mg/m² as the starting dose and had no reason to consider post-initiation dose reductions as potential starting doses.

Nor does Conroy’s “median relative dose intensity” suggest preemptive oxaliplatin dose reduction to 60 mg/m². *See* Paper 1 at 51-52. The fact that some patients’ doses were reactively reduced to 60 mg/m² after experiencing toxicity would not have motivated a POSA to preemptively initiate treatment at that reduced level—such reasoning reverses Conroy’s clear teaching to start at 85 mg/m², monitor for toxicity, and reduce only as needed.

VIII. APOTEX FAILS TO ESTABLISH A REASONABLE LIKELIHOOD THAT ANY CHALLENGED CLAIM OF THE ’552 PATENT IS OBVIOUS

A. Ground 1 (Claims 1, 3-6, 8-14): Apotex’s Asserted Combination Fails to Establish Obviousness

Apotex argues that it would have been obvious to modify FOLFIRINOX in order to arrive at the claimed combination therapy over Conroy, Conroy Protocol, Conroy Appendix, and Mahaseth in combination with Bayever, Saif, Ko, and

Cantore.^{3,4} Apotex’s allegedly obvious modifications to FOLFIRINOX consist of four distinct, hindsight-driven modifications, namely: (1) replacement of free irinotecan with liposomal irinotecan; (2) change in dosage from 180 mg/m² of free irinotecan to a dosage of 60 mg/m² of liposomal irinotecan; (3) reduction of 85 mg/m² oxaliplatin to 60 mg/m² oxaliplatin; and (4) removal of the bolus dose of 5-FU. Apotex’s expert confirmed that modification of FOLFIRINOX to arrive at the claimed method would require all four modifications. Ex. 2007 at 72:9-73:25. To prevail, Apotex must show that a POSA would have been motivated to make ***all four***

³ CSPC’s, and thus Apotex’s, petition is further deficient because each asserted ground relies on the Conroy Protocol (Ex. 1004), a French-language document for which no certified translation was provided as required by 37 C.F.R. § 42.63(b). The Board consistently denies institution where all grounds rely on references failing to comply with this rule. *See, e.g., Zhongshan Broad Ocean Motor Co., Ltd. v. Nidec Motor Corp.*, IPR2014-01123, Paper 20 at 7-8 (PTAB Jan. 21, 2015). Moreover, the uncertified translation contains apparent discrepancies—including omitted symbols and ambiguous formulas in the very sections Apotex cites for oxaliplatin dose reduction—casting further doubt on its reliability. *Compare* Ex. 2022 (Original Conroy Protocol) at 16 with Ex. 1004 at 16; *compare* Ex. 2022 (Original Conroy Protocol) at 86 with Ex. 1004 at 85-86; *compare* Ex. 2022 (Original Conroy Protocol) at 86 with Ex. 1004 at 86.

⁴ Apotex also fails to establish that the Conroy Protocol (Ex. 1004) and Conroy Appendix (Ex. 1017) qualify as prior-art printed publications. Neither document contains a publication date, and Apotex provides no evidence beyond a statement in a separate exhibit (Ex. 1003) that these documents were publicly accessible or reasonably discoverable by a POSA before the critical date. Mere assertion of “simultaneous publication” is insufficient to meet Apotex’s burden. *See Hulu, LLC v. Sound View Innovations, LLC*, IPR2018-01039, Paper 29 at 13 (PTAB Dec. 20, 2019).

of these specific modifications together with a reasonable expectation of success. Apotex's obviousness argument fails for the reasons discussed below.

1. Apotex and Dr. Ratain Ignore the Full Scope of the Prior Art, Relying Instead on Hindsight

Apotex's petition is fundamentally driven by improper hindsight. Indeed, Apotex's expert, Dr. Ratain testified that he began his analysis with FOLFIRINOX based on its "similarity" to the '552 patent claims and that his review of the '552 patent's specification and/or claim elements drove selection of other asserted references. Ex. 2007 at 29:4-20; 35:12-36:5; 39:24-41:16. This backward-looking approach—starting from the patented invention to select and combine prior art—epitomizes hindsight reasoning. Compounding this error, Apotex entirely fails to explain why a POSA would have selected FOLFIRINOX from among other available prior-art treatments, or why a POSA would have been motivated to make multiple, specific modifications to FOLFIRINOX rather than pursuing alternative approaches.

As a POSA would have been aware, the limitations of chemotherapy (e.g., FOLFIRINOX), particularly in the treatment of metastatic pancreatic cancer, motivated the pursuit of and research into other, non-chemotherapy options. A POSA would have been aware of such approaches, which included radiation therapy and personalized treatment options. *See, e.g.*, Ex. 2017 (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. 2023 (Valsecchi) at 4-5, 10. Against this backdrop (which Apotex 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 Apotex relies.

2. Apotex Identifies No Motivation to Depart from FOLFIRINOX’s “Gold-Standard” Treatment Regimen, Which Does Not Include Liposomal Irinotecan

The starting point for Apotex’s hindsight-driven argument is the FOLFIRINOX regimen described in Conroy. As Apotex describes, FOLFIRINOX was the established, “gold standard” of care in treating metastatic pancreatic cancer at the time of the invention. *See* Paper 1 at 2 (“[T]he *gold standard* of care for treating metastatic pancreatic cancer in humans who had not received previous cancer treatment (‘first-line therapy’) was . . . ‘FOLFIRINOX.’” (emphasis in original)); *see also id.* at 3, 10, 18, 35, 37, 45, 47, 49, 65 (referring to FOLFIRINOX as a “gold standard,” “established gold-standard,” or “gold-standard first-line” regimen or therapy). Dr. Ratain and Apotex’s own cited references similarly characterize FOLFIRINOX as the “gold standard” of care. For example, Dr. Ratain refers to the treatment described in Conroy as the “gold-standard FOLFIRINOX regimen for first-line treatment of metastatic pancreatic cancer.” Ex. 1002 at ¶ 232.

This is further reflected in Apotex's and Dr. Ratain's cited references. *See, e.g.*, Hatachi (Ex. 1021) at 1 ("FOLFIRINOX... is the gold-standard therapy for advanced pancreatic cancer."); Conroy 2013 (Ex. 1041) at 6 ("FOLFIRINOX is now the reference treatment in patients with good performance status and is cost-effective."). Thus, the starting point for Apotex's obviousness argument to modify the prior art is a therapy that was already considered to be the established "gold standard" of care for treatment of the claimed patient population.

Apotex 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 to arrive at the claimed invention. Apotex suggests that concerns over toxicity of the FOLFIRINOX regimen would have prompted a POSA to modify FOLFIRINOX. *See* Paper 1 at 2-3. But Dr. Ratain's testimony reveals generic, non-specific reasoning that could apply to any chemotherapy regimen:

Q: What are the proposed modifications to the FOLFIRINOX regimen that you believe were obvious to do?

A: Well, the two modifications are to make it work better and to make it less toxic. Those were the – the two goals of anybody modifying a regimen.

Ex. 2007 at 53:2-7; *see also id.* at 92:14-93:14 (testifying, generally, that "there's always a reason to make things better, and there's always concern about trying to make things better."). This generalized testimony fails to explain why a POSA

would have made the four specific modifications required to arrive at the claimed invention. As discussed *supra*, arriving at the '552 patent's claimed treatment regimen would require all four specific modifications together. Apotex fails to establish that any generic concerns of toxicity would have prompted a POSA to make this particular combination of modifications simultaneously.

As an initial matter, Apotex and Dr. Ratain take the dose-modification disclosures of Conroy, the Conroy Protocol, and the Conroy Appendix out of context. Apotex and Dr. Ratain cite Conroy's reference to the "median dose intensity" for the various FOLFIRINOX components. *See* Paper 1 at 45-46; Ex. 1002 at ¶ 69. But neither Apotex nor Dr. Ratain explains how the reported "median dose intensity" for each of the FOLFIRINOX components relates to, much less renders obvious, the claimed methods of treatment. Indeed, disclosure of dose reduction in Conroy, the Conroy Protocol, and the Conroy Appendix is in the limited context of addressing toxicity concerns. *See* Ex. 1003 at 3 (discussing dose reduction "[i]n the event of predefined toxic events"); Ex. 1004 at 15-18 (purporting to reflect dose adjustments in the event of toxic events); Ex. 1017 at 3-7 (providing "[d]osage adjustment guidelines for toxicities in the FOLFIRINOX arm"). A POSA reading Conroy, the Conroy Protocol, and the Conroy Appendix would have understood that that reduction of the oxaliplatin dose occurs in the specific context

of addressing toxicity concerns that may arise, not as a safe and efficacious first-line treatment.

Indeed, a POSA would have understood that FOLFIRINOX was the “gold standard” of first-line treatment, and that it could be modified with dosage adjustments as necessary to address toxicity concerns. Conroy identifies “protocol-specified treatment modifications” in the event of toxic events, including delayed treatment and dose reduction. Ex. 1003 at 3. Conroy reports that, of the patients who received FOLFIRINOX as part of the study, “[t]he median relative dose intensities of fluorouracil, irinotecan, oxaliplatin, and gemcitabine were 82%, 81%, 78%, and 100%, respectively.” *Id.* at 4. Despite the higher incidence of events that led to dose reduction, “a significant increase in the time to definitive deterioration of the quality of life was observed in the FOLFIRINOX group as compared with the gemcitabine group.” *Id.* at 8. A POSA would understand, based on Conroy, that FOLFIRINOX is a first-line treatment option for patients with metastatic pancreatic cancer, and that it could be modified with dose reduction as necessary to address toxicity concerns.

Other references describe modified FOLFIRINOX regimens, developed to address toxicity concerns, that entail more limited modifications than what Apotex proposes. Mahaseth (Ex. 1005), a reference that was before the Patent Office during prosecution (*see* Ex. 1001 at 5), describes a study that evaluated a modified

FOLFIRINOX regimen, which includes discontinuation of the 5-FU bolus and administration of growth factors. *See* Ex. 1005 at 1. It was hypothesized that such modification might “improve the safety profile without compromising the activity of FOLFIRINOX.” *Id.* As reported in Mahaseth, removal of the 5-FU bolus and administration of growth hormones was observed to be “well tolerated and has significant activity in metastatic [pancreatic cancer].” Ex. 1005 at 5. Alessandretti (Ex. 1044) reports that modified FOLFIRINOX (no bolus of 5-FU and reduced dose of at least one agent since first cycle) “is a therapeutic option to elderly [patients] with advanced pancreatic adenocarcinoma.” Ex. 1044 at 1. In light of this knowledge, a POSA would not have been motivated to further modify FOLFIRINOX as Apotex proposes.

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. Conroy 2013 (Ex. 1041) acknowledges modifications to address toxicity concerns, namely removal of the 5-FU bolus dose or removal of oxaliplatin (“FOLFIRI” regimen). Ex. 1041 at 2; *see also id.* at Table 1 (summarizing data from studies that evaluated modified FOLFIRINOX regimens). Ko 2011 (Ex. 1042) questions whether “all of the individual components of FOLFIRINOX [are] necessary” or whether “this combination [can] somehow be simplified to improve tolerability without compromising efficacy.” Ex. 1042 at 2.

In light of this knowledge, a POSA would have been motivated to subtract—rather than replace, as Apotex argues—chemotherapy drug components of FOLFIRINOX.

A POSA would not have understood Conroy, the Conroy Protocol, or the Conroy Appendix to teach—as Apotex suggests—a first-line combination treatment that includes, *ab initio*, a 60 mg/m² dose of oxaliplatin. Apotex identifies no prior-art reference that relies on Conroy as such. Rather, post-Conroy publications reflect an understanding that the FOLFIRINOX regimen includes 85 mg/m² oxaliplatin, with dose reduction for the limited purpose of addressing toxicity concerns that may arise. *See, e.g.*, Ex. 2011 (Marsh) at 1, 3 (Table 2). A POSA would not have been motivated, based on Apotex’s cited references, to pursue a novel combination treatment that is both well-tolerated and effective.

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. *See* Ex. 1002 at ¶¶ 65-67 (identifying only “the potential for life-threatening (and even fatal) toxicity,” providing such examples in the form of “severe and life-threatening diarrhea, neutropenia, febrile neutropenia, thrombocytopenia and sensory neuropathy”). Dr. Ratain further acknowledges that modifications to address these toxicity concerns were known. *See id.* at ¶¶ 68-82.

As Dr. Ratain describes, one such approach entailed dose reduction of one or more existing FOLFIRINOX components. *See id.* at ¶¶ 69-72. And, as discussed above, Dr. Ratain’s own cited references suggest removing—as opposed to replacing—chemotherapy drug components of FOLFIRINOX. *See* Ex. 1041 (Conroy 2013) at 1; Ex. 1042 (Ko 2011) at 2. Thus, 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.

Thus, to the extent a POSA would have sought to address toxicity concerns, the prior art already described a solution in the form of the modifications to FOLFIRINOX that were known and practiced in the art. Apotex fails to explain why a POSA would have been motivated, in spite of this knowledge, to arrive at the ’552 patent’s combination therapy by, *inter alia*, introducing a new chemotherapeutic agent (liposomal irinotecan), much less at the specifically claimed dosage, in combination with the other recited components and doses.

3. Apotex Identifies No Motivation to Introduce Liposomal Irinotecan, in the Claimed Dosage, to FOLFIRINOX or Its Known Modified Versions

As discussed, toxicity concerns would not—as Apotex and Dr. Ratain argue—have motivated a POSA to depart from the “gold-standard” FOLFIRINOX regimen and modifications to FOLFIRINOX that were known and practiced in the art. Such known modifications to FOLFIRINOX were made for the limited purpose of

addressing toxicity concerns, and none of them taught, suggested, or motivated the introduction of an entirely new chemotoxic agent (liposomal irinotecan), much less in the claimed dosage. Accordingly, a POSA would not—as Apotex argues—have been motivated to address toxicity concerns by substituting free irinotecan for liposomal irinotecan, let alone in the claimed dose.

Apart from toxicity concerns, Apotex identifies no legitimate motivation for a POSA to introduce liposomal irinotecan to the FOLFIRINOX regimen. Apotex suggests that FOLFIRINOX’s “gold-standard” status would have supplied such motivation. *See* Paper 1 at 35 (“Given that FOLFIRINOX was the gold standard of first-line treatment for metastatic pancreatic cancer patients, the POSA would have been surely motivated to replace the non-liposomal irinotecan of FOLFIRINOX with Bayer’s liposomal irinotecan.”). But a general desire to improve upon existing technology is insufficient. *See, e.g., ActiveVideo Networks, Inc. v. Verizon Communications, Inc.*, 694 F.3d 1312, 1328 (Fed. Cir. 2012) (rejecting such testimony, which “fails to explain why a person of ordinary skill in the art would have combined elements from specific references *in the way the claimed invention does*” (emphasis in original)). Especially here, where Dr. Ratain’s own testimony undermines any alleged motivation based on the properties of liposomal irinotecan. At his deposition, Dr. Ratain admitted that liposomal irinotecan is a “distinct product” from irinotecan, with “different properties.” Ex. 2007 at 49:7-12. Dr.

Ratain moreover explained that the “different properties” of liposomal irinotecan do not, in his opinion, translate to a superior approach:

[W]hat’s unclear is whether liposomal irinotecan can increase the efficacy of irinotecan. It’s just not entirely clear. . . . [I]t’s not yet been proven that this formulation or this schedule of giving irinotecan, so to speak, is superior than the more conventional, historical approach.

Id. at 50:23-51:19. Dr. Ratain confirmed that this was true as of August 21, 2015.

Id. at 51:20-24. Moreover, neither Apotex nor Dr. Ratain explains why a POSA would have been motivated to include liposomal irinotecan in combination with dose reductions of oxaliplatin and 5-FU. As Dr. Ratain testified at his deposition, “none of these drugs were ever optimized, the dosages. Nobody really knows what – you know, whether more is better is the real issue.” Ex. 2007 at 77:9-15.

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. Apotex relies heavily on knowledge of the FOLFIRINOX regimen, which has some overlap in components with the claimed therapy, in this respect. *See, e.g.*, Paper 1 at 1-3. Dr. Ratain likewise premises his obviousness opinion on the proposition that “all of the components of the FOLFIRINOX regimen (infusional 5-FU, LV, irinotecan, and oxaliplatin) had been in widespread clinical use since

2002.” Ex. 1002 at ¶ 73.⁵ But knowledge of individual components of a claimed invention does not suffice to establish motivation to combine them in the way that they are claimed. *Personal Web Technologies, LLC v. Apple, Inc.*, 848 F.3d 987, 993-94 (Fed. Cir. 2017) (noting that “a skilled artisan, once presented with the two references, would have understood that they *could be* combined . . . does not imply a motivation to pick out those two references and combine them to arrive at the claimed invention” (emphasis in original)). Thus, knowledge of FOLFIRINOX and, separately, knowledge of liposomal irinotecan does not establish requisite motivation to arrive at the ’552 patent’s invention.

Nor does Bayever’s disclosure of the properties of liposomal irinotecan supply requisite motivation. As noted in Ipsen’s discretionary denial brief, the Patent Office has already considered the issue of whether Bayever, combined with Conroy’s FOLFIRINOX, renders the ’552 patent claims obvious, and it decided that issue in Ipsen’s favor. *See* Paper 9 at 21-24. Nevertheless, Apotex cites Bayever’s disclosure of properties of liposomal irinotecan in support of obviousness. *See, e.g.*, Paper 1 at 3. But apart from toxicity concerns, Apotex fails to identify any problem that would have motivated a POSA to turn to liposomal irinotecan on the basis of

⁵ Apotex and Dr. Ratain ignore that the ’552 patent’s claimed combination therapy differs from FOLFIRINOX in both its constituent components and their dosages.

these properties, let alone in combination with the other recited components of the invention. Notably, Apotex's own expert testimony (as discussed above) undermines Apotex's purported motivation where he stated that liposomal irinotecan's purported superiority over irinotecan was not yet proven as of the priority date of the '552 patent. *See* Ex. 2007 at 49:7-12; 50:23-51:24. Nonetheless, that the claimed combination may have later been found to provide a benefit over other therapies cannot suffice as requisite motivation. *See Insite Vision Inc. v. Sandoz, Inc.*, 783 F.3d 853, 859 (Fed. Cir. 2015) ("In considering motivation in the obviousness analysis, the problem examined is not the specific problem solved by the invention. . . . Defining the problem in terms of its solution reveals improper hindsight in the selection of the prior art relevant to obviousness." (citation omitted)). Here, the only problem identified by Apotex and Dr. Ratain is toxicity, for which the prior art describes solutions that would not lead a POSA to the claimed combination therapies.

Critically, neither Apotex nor Dr. Ratain cites any motivation to introduce liposomal irinotecan to the FOLFIRINOX regimen in the specifically claimed dosage of 60 mg/m². At most, Apotex and Dr. Ratain rely on the disclosure of Bayever for use of liposomal irinotecan, generally. *See* Paper 1 at 46; Ex. 1002 at ¶¶ 235-240. But neither Apotex nor Dr. Ratain explains how or why a POSA would select the '552 patent's claimed dosage of 60 mg/m² in light of Bayever. Apotex

and Dr. Ratain also cite Saif (Ex. 1007) and Ko (Ex. 1008) for the same proposition but fail to articulate how those references teach, suggest, or motivate the specifically claimed dosage of liposomal irinotecan. *See* Paper 1 at 46; Ex. 1002 at ¶¶ 235-240. Indeed, Saif and Ko suffer from the same deficiency as Bayever in this regard, because neither concerns a combination therapy that includes oxaliplatin. Saif concerns a study involving “the combination of MM-398 with 5-fluorouracil (5-FU) and leucovorin” for second-line treatment. Ex. 1007 at 1. Ko concerns liposomal irinotecan monotherapy for second-line treatment. *See* Ex. 1008 at 1 (“Background”). Apotex and Dr. Ratain fail to explain why or how a POSA would have been motivated, based on these cited references, to arrive at the claimed dosage of liposomal irinotecan as part of a first-line combination therapy that includes each of the other claimed components (e.g., oxaliplatin), in the claimed dosages.

4. Apotex Does Not Articulate Any Reasonable Expectation of Success in Practicing the Claimed Invention

Even if Apotex presented a coherent motivation to modify FOLFIRINOX in the multiple, specific ways that it alleges would have been obvious (it does not), Apotex entirely fails to articulate a reasonable expectation of success in doing so. That is, Apotex articulates no basis to conclude that a POSA would reasonably expect each of the allegedly obvious modifications, let alone all four, to result in an antineoplastic therapy as claimed. At most, Apotex repeats the same “result-effective variable” argument over which the Patent Office has already found the ’552

patent claims patentable and attempts to distinguish this case from *OSI v. Apotex*. See Paper 1 at 50-53; *see also* Ex. 1084 at 318-320, 381; Ex. 1088 at 17-19, 61; Ex. 1097 at 3, 192-194; Ex. 1098 at 204-206; Ex. 1112 at 163-165, 183, 190; Ex. 1119 at 12-14, 144-150; Ex. 1120 at 161-163, 255. Neither argument is availing.

(a) Apotex’s “Result-Effective Variable” Argument Has Already Been Considered and Is Unavailing

Apotex argues that “lowering the dose of oxaliplatin from 85 mg/m² in FOLFIRINOX to the claimed 60 mg/m² was a ‘result effective variable’ that render[s] the claims obvious” on the grounds that “lowering the dose of oxaliplatin from 85 mg/m² to the claimed 60 mg/m² would have been routine optimization.” Paper 1 at 50-51. This argument lacks merit for several reasons.

First, and as discussed in Ipsen’s discretionary denial brief, (*see* Paper 9 at 21), there is no question that the Patent Office has already considered this argument and decided in favor of patentability. Indeed, Apotex explicitly acknowledges that the ’552 patent applicant overcame this argument during prosecution. *See* Paper 1 at 50 (“[T]he Office steadfastly maintained throughout prosecution that lowering the dose of oxaliplatin from 85 mg/m² in FOLFIRINOX to the claimed 60 mg/m² was a ‘result effective variable’ that rendered the claims obvious.”); *see also* Ex. 1097 at 194 (Feb. 27, 2020 Rejection); Ex. 1119 at 12-13 (Aug. 26, 2021 Rejection). Thus, the Patent Office has already decided this issue in Ipsen’s favor.

Second, Apotex and Dr. Ratain’s argument relies on a misunderstanding of the claimed dosage of oxaliplatin. The ’552 patent claims recite, *inter alia*, oxaliplatin in a dosage of 60 mg/m². See Ex. 1001 at claim 1. Apotex and Dr. Ratain cite Conroy’s disclosure of “a median relative dose intensity of oxaliplatin of 78% of the 85 mg/m²” in support of the allegedly obvious dose reduction. See Paper 1 at 19. But 78% of 85 mg/m² is 66.3 mg/m², not the claimed 60 mg/m². Neither Apotex 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.

Third, Apotex’s argument ignores that differences between the FOLFIRINOX regimen and the claimed combination therapy are more complex than a difference in dosage of just one component. Each regimen comprises a combination of *four separate drugs*, each in its own specific dosage. See Ex. 1001 at claim 1; Ex. 1003 at 3. The two regimens do not include the same drugs: FOLFIRINOX includes irinotecan in a dosage of 180 mg/m², whereas the ’552 patent’s regimen includes liposomal irinotecan in a dosage of 60 mg/m². See Ex. 1001 at claim 1; Ex. 1003 at 3. Apotex’s “result-effective variable” argument assumes, without basis or support, that a dosage adjustment in one regimen comprising free irinotecan in a dosage of 180 mg/m² will have the same effect as in the other, comprising liposomal irinotecan (a different drug) in a different dosage.

Apotex’s argument that oxaliplatin is a “result-effective variable” subject to routine experimentation ignores the multivariate nature of the claimed invention and relevant field. As the Federal Circuit has recently noted, “in cases with multiple result-effective variables, ‘[e]vidence that the variables interacted in an unpredictable or unexpected way could render the combination nonobvious.’” *ModernaTx, Inc. v. Arbutus Biopharma Corp.*, 18 F.4th 1364, 1376 (Fed. Cir. 2021) (citation omitted). In *ModernaTx*, the Federal Circuit held that, even if claims to compositions involving four different phospholipid components were each result-effective variables, “optimizing the four interdependent lipid components in the prior art nucleic acid-lipid particles would not have been routine, and [petitioner’s] proposed adjustments to the various lipid components are hindsight driven.” *Id.* at 1377. Similarly here, “[t]he unpredictable interactivity between the various [] components renders the claims [] nonobvious.” *Id.*

Literature indicates that, in the context of chemotherapy, the relationship between dosage and clinical effect is not straightforward. As one publication co-authored by Dr. Ratain acknowledges, inter-patient variability in response to chemotherapy drugs produces unpredictable clinical effects. *See, e.g.*, Ex. 2024 (Undevia) at 2 (“Anticancer drugs can have considerable interindividual pharmacokinetic variability, which, given the narrow therapeutic index of these

drugs, results in unpredictable clinical effects.”). Thus, inter-patient variability in response to chemotherapy is one complicating factor.

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. *See, e.g.*, Ex. 2025 (the ’350 patent) at 1:26-2:24. Another of Dr. Ratain’s publications likewise states that “[p]atients treated with irinotecan have marked variability in toxicity at standard doses.” Ex. 2026 (Ratain 2014) at 1. Literature also recognizes inter-patient variability associated with 5-FU. *See, e.g.*, Ex. 2027 (Bach) at 1 (“Despite dose correction based on body size, the degree of interpatient variation in clinical outcomes following standard doses of chemotherapy is large and plasma concentration of cytotoxic drugs may vary up to 14-fold or even 100-fold in the case of 5-fluorouracil (5-FU).”); Ex. 2028 (Gurney) at 2 (describing a study that found body surface area dosing of 5-FU resulted in variability such that “80% of patients were found to have an ineffective 5FU plasma concentration after the first dose”). Based on at least this information, a POSA would understand that dose adjustments to the components of FOLFIRINOX do not yield predictable effects.

The relationship between dose adjustment and clinical effect is even further complicated in the context of combination therapy for cancer treatment. Alnaim

(Ex. 2029), discusses challenges in therapeutic drug monitoring (TDM), i.e., evaluating the impact of drug concentrations and dosages on therapeutic outcomes, in the context of chemotherapy. *See* Ex. 2029 (Alnaim) at 1. Combination therapy, which involves the administration of two or more anti-cancer agents, presents special challenges. *See id.* at 2 (stating that combination therapy makes it “very difficult to accurately define the pharmacodynamics of each individual agent” and “also complicates the pharmacodynamics of drug toxicity”); *see also* Ex. 2027 (Bach) at 1 (“[T]he routine use of combination therapy in oncology patients makes establishing relationships between drug concentration and therapeutic end points difficult.”); *see also* Ex. 2007 at 62:12-63:15 (describing the “infinite number of possibilities” a POSA might face in assessing the maximum dose for a combination therapy). Thus, inter-patient variability in response to single-drug chemotherapy regimens are further unpredictable in the context of combination chemotherapy regimens.

Apotex’s references acknowledge the complexity of dose adjustment in the specific context of FOLFIRINOX. Masi (Ex. 1012) speculates about a potentially “synergic or additive interaction between SN-38 (the active metabolite of irinotecan), oxaliplatin and 5-FU,” but “whether a regimen combining these three agents allows their administration at optimal doses” had yet to be determined. Ex. 1012 at 1-2. Ko 2011 (Ex. 1042) suggests the unpredictable effects of dose

adjustments to FOLFIRINOX on outcomes, when used in combination with other novel agents. Ex. 1042 at 2 (“Other studies in development are adopting a similar strategy, which should allow us to discover the doses of FOLFIRINOX that can safely be combined with these newer agents, or whether its dosing will be reduced to the extent that efficacy is potentially compromised.”). A POSA would have understood, in light of this information, that dose adjustment in one therapeutic regimen may not produce the same effect when undertaken in another, let alone when an entirely new ingredient (i.e., liposomal irinotecan) is introduced as here.

Other references cited by Apotex underscore the challenges in arriving at appropriate doses for a new combination therapy. Hamberg (Ex. 1046), of which Dr. Ratain is a co-author, states that “[d]etermining the best dose for new combination drug treatments will have to be balanced against” a number of aspects, among them: (1) “the increasing diversity of classes of agents and mechanisms of action”; (2) continuous administration versus intermittent administration; (3) and “safety profiles that are completely different from those of conventional cytotoxic agents.” Ex. 1046 at 1. For these reasons, Hamberg discusses numerous points for consideration in designing Phase I trials of combination therapies. *See generally* Ex. 1046.

Nor are the dose modifications of the Conroy Protocol and the Conroy Appendix a straightforward adjustment of a single variable. As can be seen in the

very section of the Conroy Protocol that Apotex cites, toxicity events that call for a dose reduction of oxaliplatin (highlighted in yellow below) *also* call for dose reductions in other components (highlighted in green below):

6.3.1 Hematological toxicity

6.3.1.1 According to biological results at D15

TREATMENT A: Folfirinox

CBC at D15	CYCLE DELAY	DOSE REDUCTION		
		Irinotecan (CPT-11)	Oxaliplatin (L-OHP)	LV5FU
PNN $\geq 1.5 \times 10^3/L$ and platelets $\geq 75 \times 10^3/L$	No cycle delay	No dose reduction		
PNN $< 1.5 \times 10^3/L$	Delay treatment until PNN 1,500 (until D22 or D29 if necessary). If no recovery at D29, discontinuation of treatment*	1 st episode: dose reduction to 150 mg/m² 2 nd episode: dose maintained at 150 mg/m ² 3 rd episode: discontinuation of treatment	1 st episode: no dose reduction 2 nd episode: reduce dose to 60 mg/m² 3 rd episode: discontinuation of treatment	1 st episode: eliminate bolus on D1
Platelets $< 75 \times 10^3/L$	Delay treatment until recovery (platelets $\geq 75 \times 10^3/L$) If no recovery at D29, discontinuation of treatment	1 st episode: no dose reduction 2 nd episode: reduce dose to 150 mg/m² 3 rd episode: discontinuation of treatment	1 st episode: reduce dose to 60 mg/m² 2 nd episode: maintenance of reduced dose 3 rd episode: discontinuation of treatment	1 st 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 (Conroy Protocol) at 16. The variety of possible dose adjustments arising from different toxicity events, combined with the inter-patient variability in response, underscore the complex nature of dose modification of this combination therapy.

(b) Likelihood of Success in the Relevant Field Is Particularly Low

Despite Apotex's argument to the contrary, this case is analogous to *OSI v. Apotex*, in which low success rates in the relevant field supported a finding of non-obviousness. *See OSI Pharms., LLC v. Apotex, Inc.*, 939 F.3d 1375, 1385 (Fed. Cir. 2019). In *OSI v. Apotex*, the Federal Circuit reversed a PTAB determination of obviousness, relying in part on evidence of particularly low success rates in developing new cancer treatments. *See id.* As discussed below, the likelihood of success here in developing new treatments for metastatic pancreatic cancer is even lower, which likewise supports non-obviousness of the claimed methods.

Indeed, the success rate for oncology drugs remains the lowest of all therapeutic areas, particularly in the field of pancreatic cancer. A study of clinical development success rates from 2006 to 2015 reports that, of all disease areas, oncology had the lowest likelihood of approval (5.1%) from Phase I. Ex. 2030 (BIO study) at 3. And, within oncology, the Phase III failure rate for new pancreatic cancer treatments is the highest—higher than even NSCLC, the type of cancer addressed in *OSI v. Apotex*. *See* Ex. 2031 (Thota) at 4 (“The failure rate of phase III clinical trials in advanced pancreatic cancer is high (87%).”); Ex. 2030 (BIO study) at 14 (reporting NSCLC has having the fourth-lowest Phase III success rate, and pancreatic cancer as having the lowest); *see also id.* at 15 (“Solid tumor drugs for pancreatic cancer seemed to have the toughest challenges in Phase III studies

(13.1%, n=15).”). Here, as in *OSI v. Apotex*, the unpredictability of cancer treatment and extremely low success rate for new treatments undermines any claim of reasonable expectation of success.

To the extent that Apotex and Dr. Ratain cite any prior-art teachings on liposomal irinotecan’s potential as part of the claimed combination therapy, the teachings are limited to preclinical or otherwise early-stage clinical data concerning a treatment regimen directed to a different disease and/or patient population. Apotex and Dr. Ratain argue that “Bayever and other prior art disclosed evidence of superiority of liposomal irinotecan to irinotecan.” Ex. 1002 at ¶ 236 (citing Ex. 1006 at 11, 19-21, 25; Ex. 1008 at 2-5; Exs. 1058-1059); *see also* Paper 1 at 46-47. Dr. Ratain’s cited portions of Bayever (Ex. 1006) describe pharmacokinetic properties of liposomal irinotecan relative to free irinotecan, data from preclinical studies, and a proposed three-drug (unlike the ’552 patent’s four-drug) regimen of liposomal irinotecan in combination with leucovorin and 5-FU for a study in second-line (not first-line) treatment of pancreatic cancer patients. Ex. 1006 at 11, 19-21, 25. However, as stated above, Dr. Ratain testified that liposomal irinotecan was a distinct product from irinotecan whose superiority was not yet proven as of the priority date of the ’552 patent. *See* Ex. 2007 at 49;7-12; 50:23-51:24. Apotex also cites Ko (Ex. 1008), which summarizes preclinical study results and describes the results of a Phase II study of the three-drug combination described in Bayever. Ex.

1008 at 2-5. Finally, Apotex cites Kim (Ex. 1058) and Hann (Ex. 1059), which describe the results of preclinical studies conducted in animals. *See* Ex. 1058, Ex. 1059. Apotex relies on Dr. Ratain for the predictive value of such data. *See* Paper 1 at 51 (“As Dr. Ratain further explains, it would have been fully expected that given what was known about MM-398 liposomal irinotecan’s pre-clinical profile to remain at the tumor site longer than free-irinotecan (as disclosed in Bayever), lowering the dose of oxaliplatin . . . would have been routine optimization.”). Apotex’s arguments regarding the expectations of a POSA are therefore based on preclinical data or otherwise early-stage clinical data.

By its expert’s own admission, however, such early-stage data is not predictive of success in the field of this invention. Paller (Ex. 1045), a reference co-authored by Dr. Ratain, explicitly states that “[t]he level of preclinical data required to predict a benefit in clinical trials is currently unknown, because preclinical studies do not generally predict success of clinical trials.” *See* Ex. 1045 at 2. Hamberg (Ex. 1046), another reference co-authored by Dr. Ratain, also acknowledges the complexities and challenges specifically associated with early-stage trials of combination therapies. *See* Ex. 1046 at 9 (“Combination phase I studies are extremely complex.”); *see also* Ex. 1045 (“The design and conduct of the phase I combination trial present specific challenges, such as the optimum selection of agents to combine among the range of possible combinations; the selection of the

appropriate dose and schedule (including which drug or drugs to dose escalate); drug-drug interactions; overlapping toxicities; and logistical and regulatory challenges.”). Another of Dr. Ratain’s publications states that “it’s 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).” Ex. 2032 (Ratain 2005) at 1 (emphasis added); *see also* Ex. 2023 (Valsecchi) at 6-8 (discussing negative trials—a biological rationale for further study does not equate to a reasonable expectation of success). Thus, the data cited by Apotex in support of obviousness does not create any reasonable expectation of success in practicing the claimed methods.

5. Unexpected Results Further Support Non-Obviousness of the Claimed Combination Therapy

As discussed in Ipsen’s discretionary denial brief, (*see* Paper 9 at 24-28), unexpected results properly support non-obviousness of the claimed methods. Apotex’s critiques of the evidence of unexpected results submitted during prosecution are that the evidence: (1) suffers from “inherent limitations” and improperly invites a cross-trial comparison of efficacy results; and (2) is “refuted” by more recent publications that purport to show “identical efficacy” between the study of Conroy and the study cited by the ’552 patent applicant. *See* Paper 1 at 36-38. Apotex’s critiques fail.

Apotex mischaracterizes the '552 patent applicant's statements relating to unexpected results made during prosecution. Specifically, Apotex ignores that the '552 patent applicant submitted evidence of unexpected results in the form of "tolerability *and* efficacy," not simply superior efficacy over FOLFIRINOX. *See* Ex. 1119 at 149-150 ("Indeed, none of the references teach or suggest tolerability *and* efficacy of 60 mg/m² oxaliplatin in combination with the claimed liposomal irinotecan, oxaliplatin, leucovorin, and 5-FU dosages." (emphasis in original)). Regardless, the examiner is presumed to have read the references submitted by '552 patent applicant and drawn his own conclusions. *See, e.g., Johnson & Johnson Surgical Vision, Inc. v. Alcon Inc.*, IPR2021-00898, Paper 17 at 34-35 (PTAB Nov. 9, 2021) (denying institution, based in part on the rationale that the examiner is presumed to have read references before the Patent Office during prosecution); *cf. BlephEx, LLC v. Myco Indus., Inc.*, 24 F.4th 1391 at 1402 ("[T]he patent examiner is presumed to have considered" references "cited on the face of the [] patent."). Again, Apotex reargues issues that have already been before the Patent Office and decided in Ipsen's favor.

To the extent that Apotex suggests that post-filing evidence of unexpected results cannot support patentability, that is incorrect. Apotex makes repeated reference to the "post-filing" evidence of unexpected results submitted during prosecution. Paper 1 at 37, 38, 54. But 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.” *Sanofi-Aventis Deutschland GmbH v. Glenmark Pharms. Inc., USA*, 748 F.3d 1354, 1360 (Fed. Cir. 2014); *see also Knoll Pharm. Co., Inc. v. Teva Pharms. USA, Inc.*, 367 F.3d 1381, 1385 (Fed. Cir. 2004) (“Evidence developed after the patent grant is not excluded from consideration, for understanding of the full range of an invention is not always achieved at the time of filing the patent application.”). The ’552 patent applicant properly relied on post-filing evidence of the claimed methods’ clinical effects to support patentability.

Apotex attempts but fails to refute the ’552 patent applicant’s evidence of unexpected results. In attempting to do so, Apotex argues that Nichetti (Ex. 1010) and Nevala-Plagemann (Ex. 1011) show “*identical* efficacy” between FOLFIRINOX and the ’552 patent’s claimed methods, i.e., NALIRIFOX. *See* Paper 1 at 37-38 (emphasis in original); *see also id.* at 55-56. But as discussed in Ipsen’s discretionary denial brief, (*see* Paper 9 at 24-26), these references amount to cross-trial comparisons that Apotex itself argues are inherently unreliable. *See* Paper 1 at 37.

Regardless, neither of Apotex’s cited references even purport to establish—as Apotex 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. *See* Ex. 1010 at 9; *see also id.* at 10 (section titled, “Limitations”). To the extent that the findings of Nichetti suggest comparative efficacy between NALIRIFOX and FOLFIRINOX, they also indicate differences in toxicity. *See* Ex. 1010 at 9. Nichetti concludes, at most, that its findings “may empower a more careful evaluation of these regimens.” Ex. 1010 at 10. Nevala-Plagemann is an opinion piece that purports to compare data from different clinical studies. *See* Ex. 1011. At most, Nevala-Plagemann purports to identify issues for future consideration and study. *See id.* at 2 (concluding that further research is needed to assess the benefit of NALIRIFOX over existing treatment options). Neither Nichetti nor Nevala-Plagemann establishes that NALIRIFOX and FOLFIRINOX are “identical” in efficacy, or in any other respect. Nor do they refute evidence that the ’552 patent’s claimed methods offer unexpected benefits.

Far from “refuting” the unexpected benefits of the invention, recent publications (which Apotex does not cite) affirm clinical benefits of the ’552 patent’s claimed NALIRIFOX regimen. Based on an analysis of oncologic benefits and costs of NALIRIFOX vs. FOLFIRINOX, one recently published study found that 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 months vs. 10.95 months). Ex. 2033 (Jiao) at 1. The same study concludes that “[t]he economic value for use of NALIRIFOX is very high and outside of any conventional boundary of acceptable value threshold for treatment.” *Id.* Another study undertook a similar comparative evaluation and concluded that, compared to FOLFIRINOX and a gemcitabine + nab-paclitaxel regimen, “NALIRIFOX was associated with the highest LYs [(life-years)], QALYs [(quality-adjusted life-years)], and cost.” Ex. 2034 (Xiang) at 1. According to these findings, and consistent with the ’552 patent applicant’s arguments during prosecution, the claimed NALIRIFOX regimen offers unique clinical benefits.

Other recent publications suggest the superiority of the ’552 patent’s NALIRIFOX regimen over FOLFIRINOX. As reported in one such recently published 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. 2035 (Cockrum). This suggests, directly contrary to Apotex’s argument, that NALIRIFOX offers clinical benefits over that of FOLFIRINOX.

Other recent publications indicate that NALIRIFOX has demonstrated superiority in a first-line setting, specifically where a modified FOLFIRINOX regimen has failed. As reported in Wainberg 2023, the NAPOLI 3 trial demonstrated

that “the NALIRIFOX regimen demonstrated statistically significant and clinically meaningful improvements in overall survival and progression-free survival compared with nab-paclitaxel and gemcitabine in patients with metastatic pancreatic ductal adenocarcinoma who had not previously received treatment in the metastatic setting.” Ex. 2036 (Wainberg 2023) at 6. By contrast, data from two trials (PASS-01 and GENERATE) recently showed that a modified FOLFIRINOX regime failed to show superiority to the same comparator, i.e., nab-paclitaxel and gemcitabine (GnP). *See* Ex. 2013 (Skorupan) at 3 (“In PASS-01, the still-maturing data show that GnP is superior to mFFX; similarly, the GENERATE study, which was designed to establish the superiority of mFFX . . . over GnP, closed early for futility.”); Ex. 2037 (Kobayashi) at 1 (concluding that “GnP is recommended as the first-line treatment for [patients] with [metastatic pancreatic cancer] compared to mFOLFIRINOX”); Ex. 2038 (Knox) at 1 (reporting that “[m]edian OS [] was 9.7 mo with GnP and 8.4 mo with mFFX”). In short, “NALIRIFOX led to better outcomes than GnP, but [a modified FOLFIRINOX regimen] failed to do so.” Ex. 2013 (Skorupan) at 3. These recent developments contradict Apotex’s assertion that the claimed NALIRIFOX regimen offers no benefits over that of FOLFIRINOX.

Thus, as the ’552 patent applicant properly argued and showed before the Patent Office, unexpected results support non-obviousness of the claimed methods.

B. Ground 2 (Claims 2, 7, and 15): Masi and Ginocchi, in Combination with Apotex's Collection of References from Ground 1, Do Not Establish Obviousness

Apotex argues that the '552 patent's claim 2—which requires that each administration of oxaliplatin begin two hours after each administration of liposomal irinotecan—is obvious for the same reasons presented for claim 1 and further in view of Bayever (Ex. 1006), Masi (Ex. 1012) and Ginocchi (Ex. 1016). *See* Paper 1 at 62. There is no dispute that none of Apotex's asserted references recite—as required by claim 2—that oxaliplatin is administered 2 hours after liposomal irinotecan. *See* Paper 1 at 62. And Apotex's obviousness challenge of claim 2 is entirely unsupported by expert testimony. Ex. 2007 at 22:12-20 (Dr. Ratain admitting that he does not opine on claim 2)⁶. Apotex's cited references suffer from additional deficiencies, as discussed below.

As an initial matter, Apotex entirely fails to address the fact that its lead reference teaches—contrary to the recited sequence—administration of oxaliplatin before administration of irinotecan. Specifically, Conroy states 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

⁶ Nor does Dr. Ratain discuss Masi or Ginocchi in connection with Ground 2. *See* Ex. 1002 at ¶¶ 308-311.

minutes, of irinotecan at a dose of 180 mg per square meter, given as a 90-minute intravenous infusion through a Y-connector.” Ex. 1003 at 3. Apotex does not even attempt to address this discrepancy.

Bayever does not support Apotex’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. Apotex relies on Bayever’s alleged disclosure that “liposomal irinotecan MM-398 should be administered first before any other drugs.” Paper 1 at 62. The only citation to Bayever that Apotex provides in this respect is to claim 4, which recites, “The method of claim 3, wherein, in each cycle, the liposomal irinotecan is administered prior to the leucovorin and the leucovorin is administered prior to the 5-FU.” Ex. 1006 at 54 (claim 4). To the extent that Bayever discloses anything regarding sequence of administration, it is with respect to liposomal irinotecan, leucovorin, and 5-FU, not “any other drugs.”

Masi does not support Apotex’s argument, because it does not concern liposomal irinotecan or the treatment of metastatic pancreatic cancer. Masi concerns treatment of a different cancer entirely, specifically metastatic colorectal cancer. Ex. 1012 at 1. The rationale underlying the sequencing described in Masi is based on observations from an “*in vitro* study on two human colon cell lines” involving free irinotecan and oxaliplatin. *See* Ex. 1012 at 5. This rationale does not concern the

claimed disease state or the potential effect of liposomal irinotecan in combination, let alone in any particular sequence, with any other drug. Apotex 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). *See* Paper 1 at 62. Masi does not inform a POSA's motivation with respect to the claimed therapy, much less with any reasonable expectation of success.

Ginocchi does not support Apotex's argument, because it does not concern liposomal irinotecan or disclose the claimed sequence. Ginocchi describes a study that evaluated a modified FOLFIRINOX regimen, but does not specify the claimed sequence of administration. At most Ginocchi states that "[t]he 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 at 1. If anything Ginocchi indicates—as discussed *supra*—that a POSA would have been aware of modifications to FOLFIRINOX capable of addressing toxicity concerns.

Apotex argues that claim 7—which requires administration of each of the four recited drugs in a particular order—is obvious for essentially the same reasons as presented for claims 1 and 2. *See* Paper 1 at 63. Apotex additionally cites “the fact

that Conroy and Mahaseth both disclose that 5-FU is administered last in the FOLFIRINOX regimen with leucovorin immediately preceding it and that Bayever also discloses that 5-FU is administered last with leucovorin immediately preceding it.” *Id.* Apotex’s arguments fail for the same reasons discussed with respect to claims 1 and 2.

None of Apotex’s cited references disclose a treatment regimen that comprises the four recited drugs, much less in the order of administration recited by claim 7. Conroy (Ex. 1003) and Mahaseth (Ex. 1005) do not contain any teaching, suggestion, or motivation with respect to a combination therapy that includes liposomal irinotecan, much less the order in which liposomal irinotecan is administered with other drugs. To the extent that Bayever discusses an order of administration, it is in the context of a three-drug combination therapy that does not include—as the ’552 patent claimed therapy does—oxaliplatin. A POSA would not be motivated based on these references to pursue the claimed combination therapies, in the recited order of administration.

Apotex argues that claim 15—which requires administration of the recited drugs in an order and also comprises administration of a corticosteroid and an anti-emetic prior to antineoplastic therapy—is obvious for essentially the same reasons as presented for claims 1 and 2 and in further view of Bayever. Apotex relies on Bayever’s alleged disclosure of administration of dexamethasone, which is a

corticosteroid, and an anti-emetic prior to antineoplastic therapy. *See* Paper 1 at 63. Apotex also cites testimony by Dr. Ratain, which conclusorily states that such administration was “known to a POSA” and “standard medical practice.” *See* Ex. 1002 at ¶¶ 310-311. Apotex’s argument fails for the reasons already discussed with respect to Ground 1.

C. Ground 3 (Claims 1-15): Carnevale and Dean Are Not Prior Art and, In Any Event, Do Not Render the Claims Obvious—Alone or in Combination with Apotex’s Other Asserted References

Apotex argues obviousness based on an effective date of November 10, 2017, relying on arguments presented for Grounds 1 and 2, as well as Carnevale (Ex. 1013) and Dean (Ex. 1014). For reasons discussed *supra*, the ’552 patent is entitled to an effective filing date of August 21, 2015. As such, Carnevale and Dean are not prior art, and Apotex’s arguments fail for the reasons discussed with respect to Grounds 1 and 2. Regardless, Apotex’s arguments based on Carnevale and Dean also fail for the reasons discussed below.

The underlying assumption for Apotex’s argument is that the ’552 patent claims require a showing of “clinical efficacy,” but neither Carnevale nor Dean even purport to describe efficacy of the ’552 patent’s claimed therapies. Carnevale summarizes studies involving liposomal irinotecan, none of which evaluate the specifically claimed, four-drug combination therapy of the ’552 patent. *See* Ex. 1013. At most, Carnevale restates the results of the study described in Ko (Ex.

1008), a Phase II study of liposomal irinotecan as a monotherapy, and that in Saif (Ex. 1007), a Phase III study of a three-drug combination therapy that does not include oxaliplatin. *See* Ex. 1013 at 7 (restating Ko), 8 (restating Saif). Dean discloses the initiation of a Phase II study of a combination therapy comprising liposomal irinotecan, oxaliplatin, leucovorin, and 5-FU, but it does not disclose the dosage of any component. *See* Ex. 1014. Thus, Dean does not disclose the claimed therapies, much less their “clinical efficacy.” Neither Carnevale nor Dean render the ’552 patent claims obvious, especially if such claims require a “clinical efficacy” component.

Carnevale moreover supports the low likelihood of success in developing new treatments for metastatic pancreatic cancer. Carnevale describes, for instance, that “progress in the therapeutic development of this disease has historically taken a slow and painstaking course, *littered with numerous negative trial results.*” Ex. 1013 at 1 (emphasis added). Carnevale further characterizes pre-2010 efforts as a “stretch of failed or clinically inconsequential trials.” *Id.* at 2. Carnevale’s characterization is consistent with a POSA’s particularly low expectations of success in the relevant field and endeavor, further supporting non-obviousness of the ’552 patent’s claimed methods.

IX. CONCLUSION

For the foregoing reasons the Board should deny institution of this petition.

Date: December 12, 2025

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CERTIFICATE OF LENGTH (37 C.F.R. §§ 42.24(D))

The undersigned hereby certifies that, according to the word-processing system used to prepare the foregoing document, this document has 13,056 words and thus complies with the applicable word limit.

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CERTIFICATE OF SERVICE (37 C.F.R. §§ 42.6(E), 42.105(A))

The undersigned hereby certifies that on December 12, 2025 copies of the foregoing document and supporting exhibits were served upon the following parties via electronic mail, with a copy to irinotecan@steptoe.com:

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