

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

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

v.

IPSEN BIOPHARM LTD.,
Patent Owner.

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

PATENT OWNER'S PRELIMINARY RESPONSE

TABLE OF CONTENTS

	<u>Page</u>
I. INTRODUCTION	1
II. BACKGROUND	2
III. THE '552 PATENT	4
IV. PERSON OF ORDINARY SKILL IN THE ART	5
V. CLAIM CONSTRUCTION	6
A. The Proper Construction of “Treat” / “Treating” is Its Plain and Ordinary Meaning	7
B. CSPC’s First Proposed Construction of “Treat” / “Treating”	8
C. CSPC’s Second Proposed Construction of “Treat” / “Treating”	12
VI. THE '552 PATENT CLAIMS HAVE AN EFFECTIVE FILING DATE OF AUGUST 21, 2015	13
VII. CSPC’s Petition Fails to Comply with Statutory Requirements	15
A. CSPC Fails to Identify All Real Parties-in-Interest	15
B. CSPC’s Non-Compliance with 37 C.F.R. § 42.63 Bars Reliance on the Conroy Protocol	16
C. CSPC Fails to Establish the Conroy Protocol and the Conroy Appendix Are Publicly Accessible Prior Art	20
VIII. CSPC FAILS TO ESTABLISH A REASONABLE LIKELIHOOD THAT ANY CHALLENGED CLAIM OF THE '552 PATENT IS OBVIOUS	23
A. Ground 1 (Claims 1, 3-6, 8-14): CSPC’s Asserted Combination Fails to Establish Obviousness	23
1. CSPC and Dr. Ratain Ignore the Full Scope of the Prior Art, Relying Instead on Hindsight	24
2. CSPC Identifies No Motivation to Depart from FOLFIRINOX’s “Gold-Standard” Treatment Regimen, Which Does Not Include Liposomal Irinotecan	25
3. CSPC Identifies No Motivation to Introduce Liposomal Irinotecan, in the Claimed Dosage, to FOLFIRINOX or Its Known Modified Versions	31

4.	CSPC Does Not Articulate Any Reasonable Expectation of Success in Practicing the Claimed Invention	35
(a)	CSPC’s “Result-Effective Variable” Argument Has Already Been Considered and Is Unavailing	36
(b)	Likelihood of Success in the Relevant Field Is Particularly Low	42
5.	Unexpected Results Further Support Non-Obviousness of the Claimed Combination Therapy	46
B.	Ground 2 (Claims 2, 7, and 15): Masi and Ginocchi, in Combination with CSPC’s Collection of References from Ground 1, Do Not Establish Obviousness.....	51
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 CSPC’s Other Asserted References	55
IX.	CONCLUSION.....	57
	CERTIFICATE OF LENGTH (37 C.F.R. §§ 42.24(D)).....	59
	CERTIFICATE OF SERVICE (37 C.F.R. §§ 42.6(E), 42.105(A)).....	60

TABLE OF AUTHORITIES

	<u>Page</u>
<u>Cases</u>	
<i>Acceleration Bay, LLC v. Activision Blizzard Inc.</i> , 908 F.3d 765 (Fed. Cir. 2018)	21, 22
<i>ActiveVideo Networks, Inc. v. Verizon Communications, Inc.</i> , 694 F.3d 1312 (Fed. Cir. 2012)	32
<i>Allergan, Inc. v. Sandoz Inc.</i> , 796 F.3d 1293 (Fed. Cir. 2015)	14
<i>Apple Inc. v. Masimo Corp.</i> , No. 2022-1890, 2024 WL 137336 (Fed. Cir. Jan. 12, 2024).....	9
<i>Applications in Internet Time, LLC v. RPX Corp.</i> , 897 F.3d 1336 (Fed. Cir. 2018)	15
<i>Ariad Pharm., Inc. v. Eli Lilly & Co.</i> , 598 F.3d 1336 (Fed. Cir. 2010)	13, 14
<i>BlephEx, LLC v. Myco Indus., Inc.</i> , 24 F.4th 1391	47
<i>Bumble Bee Foods, LLC v. Kowalski</i> , IPR2014-00224, Paper 18 (PTAB June 5, 2014)	18
<i>Hulu, LLC v. Sound View Innovations</i> , LLC, IPR2018-01039, Paper 29 (PTAB Dec. 20, 2019).....	21
<i>Insite Vision Inc. v. Sandoz, Inc.</i> , 783 F.3d 853 (Fed. Cir. 2015)	34
<i>Johnson & Johnson Surgical Vision, Inc. v. Alcon Inc.</i> , IPR2021-00898, Paper 17 (PTAB Nov. 9, 2021).....	47
<i>Knoll Pharm. Co., Inc. v. Teva Pharms. USA, Inc.</i> , 367 F.3d 1381 (Fed. Cir. 2004)	47
<i>In re Lister</i> , 583 F.3d 1307 (Fed. Cir. 2009)	21

<i>ModernaTx, Inc. v. Arbutus Biopharma Corp.</i> , 18 F.4th 1364 (Fed. Cir. 2021)	38
<i>Novartis Pharms. Corp. v. Actavis, Inc.</i> , No. 12-366, 2013 WL 6142747 (D. Del. Nov. 21, 2013).....	11
<i>OSI Pharms., LLC v. Apotex, Inc.</i> , 939 F.3d 1375 (Fed. Cir. 2019)	42, 43
<i>Personal Web Technologies, LLC v. Apple, Inc.</i> , 848 F.3d 987 (Fed. Cir. 2017)	33
<i>Pfizer Inc. v. Teva Pharms. USA, Inc.</i> , 803 F. Supp. 2d 397 (E.D. Va. 2011)	11
<i>Phillips v. AWH Corp.</i> , 415 F.3d 1303 (Fed. Cir. 2005) (en banc)	6, 9
<i>Samsung Elecs. Co., Ltd. v. Infobridge Pte. Ltd.</i> , 929 F.3d 1363 (Fed. Cir. 2019)	22
<i>Sanofi-Aventis Deutschland GmbH v. Glenmark Pharms. Inc., USA</i> , 748 F.3d 1354 (Fed. Cir. 2014)	47
<i>Shenzhen Aurora Tech. Co., Ltd. v. Putco, Inc.</i> , IPR2020-00670, Paper 10 (PTAB Aug. 27, 2020).....	18
<i>Shenzhen Kean Silicone Prod. Co., Ltd. v. PKOH NYC, LLC</i> , IPR2017-01327, Paper 14 (PTAB Dec. 6, 2017)	18
<i>Symantec Corp. v. Trustees of Columbia Univ.</i> , IPR2015-00371, Paper 13 (PTAB June 17, 2015)	21
<i>Vitronics Corp. v. Conceptronic, Inc.</i> , 90 F.3d 1576 (Fed. Cir. 1996)	6, 9
<i>Vivid Techs., Inc. v. Am. Sci. & Eng'g, Inc.</i> , 200 F.3d 795 (Fed. Cir. 1999)	7
<i>Zhongshan Broad Ocean Motor Co., Ltd. v. Nidec Motor Corp.</i> , IPR2014-01123, Paper 20 (PTAB Jan. 21, 2015)	17

Statutes

35 U.S.C. § 282(b)	6
35 U.S.C. § 312(a)(2).....	15

Other Authorities

37 C.F.R. § 42.8(b)(1).....	15
37 C.F.R. § 42.63	16, 18
37 C.F.R. § 42.63(b)	17, 18, 20
37 C.F.R. § 42.100(b)	6

LIST OF EXHIBITS

Exhibit	Description
Ex. 2014	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. 2015	Marvin Schober, et al., <i>New Advances in the Treatment of Metastatic Pancreatic Cancer</i> , Digestion, 92(3):175-184 (2015) (“Schober”)
Ex. 2006	Maria L. Rossi et al., <i>Therapeutic options for the management of pancreatic cancer</i> , 20(32) World J. Gastroenterol. 11142 (2014) (“Rossi”)
Ex. 2016	File History of U.S. Patent No. 11,344,552, Feb. 25, 2022 Remarks (“February 25, 2022 Remarks”)
Ex. 2017	Dorland’s Illustrated Medical Dictionary (32nd ed. 2012) (“Dorland’s Dictionary”)
Ex. 2018	Stedman’s Medical Dictionary for the Health Professions and Nursing (7th ed. 2012) (“Stedman’s Dictionary”)
Ex. 2019	Taber’s Cyclopedic Medical Dictionary (22nd ed. 2013) (“Taber’s Dictionary”)
Ex. 2020	Conjupro Biotherapeutics, Inc. et al, Answer to Complaint for Patent Infringement, Affirmative Defenses and Counterclaims, No. 1:24-cv-04991-RMB-MJS (July 8, 2024 D.N.J.) (“CSPC’s Answer”)
Ex. 2021	CSPC Pharmaceutical Group Limited, Voluntary Announcement, <i>Exclusive License Agreement with Cipla USA, Inc. for Irinotecan Liposome Injection</i> , May 15, 2025 (“CSPC Press Release”)
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. 2007	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. 2004	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”)

Exhibit	Description
Ex. 2023	Samir D. Undevia, et al., <i>Pharmacokinetic Variability of Anticancer Agents</i> , Nat Rev Cancer, 5(6):447-458 (2005) (“Undevia”)
Ex. 2024	U.S. Patent No. 7,807,350 to Ratain et al. (“the ’350 patent”)
Ex. 2025	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. 2026	Dylan M. Bach, et al., <i>Therapeutic drug monitoring in cancer chemotherapy</i> , Bioanalysis. 2010 May;2(5):863-79 (“Bach”)
Ex. 2027	H Gurney, et al., <i>How to calculate the dose of chemotherapy</i> , Br J Cancer 86, 1297–1302 (2002) (“Gurney”)
Ex. 2028	Alnaim, <i>Therapeutic Drug Monitoring of Cancer Chemotherapy</i> , J Oncol Pharm Pract., 13(4):207-221 (2007) (“Alnaim”)
Ex. 2008	Biotechnology Innovation Organization et al., <i>Clinical Development Success Rates 2006-2015</i> (2016) (“BIO study”)
Ex. 2009	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. 2029	Xiayu Jiao, et al., <i>Comparative effectiveness of NALIFIROX vs. FOLFORINOX in pancreatic cancer</i> , JCO 42, 4160-4160(2024) (“Jiao”)
Ex. 2030	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”)
Ex. 2031	Paul Cockrum et al., <i>Overall survival (OS) of patients with metastatic pancreatic ductal adenocarcinoma (mPDAC) treated with first-line (1L) FOLFIRINOX (FFX): Bridging the gap between the NAPOLI 3 trial and real-world practice</i> , JCO 43, 690-690 (2025) (“Cockrum”)
Ex. 2032	Zev A. Wainberg, et al., <i>NALIRIFOX versus nab-paclitaxel and gemcitabine in treatment-naive patients with metastatic pancreatic ductal adenocarcinoma (NAPOLI 3): a randomised, open-label, phase 3 trial</i> , Lancet. 2023 Oct 7;402(10409):1272-1281 (2023) (“Wainberg 2023”)

Exhibit	Description
Ex. 2033	Nebojsa Skorupan et al., <i>First-Line Treatment of Metastatic Pancreatic Ductal Adenocarcinoma: Did 2024 Offer New Insights?</i> , ASCO Daily News, available at https://dailynews.ascopubs.org/doi/full/10.1200/JCO.2024.42.1527P (“Skorupan”)
Ex. 2034	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. 2035	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 CSPC Pharmaceutical Group Limited, CSPC Ouyi Pharmaceutical Co., Ltd., and Conjupro Biotherapeutics, Inc. (collectively, “CSPC”). A Notice of Filing Date Accorded was entered on February 25, 2025. Paper 5. As set forth herein, CSPC fails to show a reasonable likelihood that it will prevail in showing that any claim of U.S. Patent No. 11,344,552 (“the ’552 patent”) is obvious.

As discussed in Ipsen’s discretionary denial brief, CSPC merely reiterates the same obviousness arguments, based on the same lead references, that the Patent Office has already considered. The Patent Office ultimately decided those arguments in Ipsen’s favor, and the Board should deny CSPC’s petition on those grounds alone.

To the extent that CSPC purports to present new arguments in its petition, those arguments fail. CSPC fails to substantiate either the Conroy Protocol or the Conroy Appendix—references upon which all of its asserted grounds rely—as prior art. CSPC moreover bases its argument on FOLFIRINOX, which it repeatedly describes as the “gold standard” of care in the relevant field, and allegedly obvious modifications thereto. But CSPC fails establish why—even assuming the absence of a “clinical efficacy” requirement—a person of ordinary

skill in the art at the time of the invention (“POSA”) would have been motivated to depart from the “gold standard” of care, much less in ways that might lead to the claimed invention. As discussed herein, CSPC’s own references teach that prior-art methods adequately address the only motivating factor that CSPC identifies, and those methods do not lead to the claimed invention. CSPC also ignores the low likelihood of success in the field, which is reflected in publications authored by its own expert. For at least these reasons, the Board should decline to institute proceedings.

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. 2014 (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. 2015 (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. 2006 (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. 2015 (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 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 CSPC reiterates in its petition. As discussed in Ipsen's discretionary denial brief, the '552 patent applicant overcame obviousness rejections that were based on Conroy (Ex. 1003) and Bayever (Ex. 1006), the same two lead references that CSPC now relies upon here. 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

CSPC and 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, CSPC 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 CSPC’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, CSPC 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. 2016 (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. 2017 (Dorland's Dictionary) at 3;

see also Ex. 2018 (Stedman’s Dictionary) at 3 (“Medical or surgical management of a patient.”); Ex. 2019 (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.

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 CSPC’s proposed construction, which does not require actual efficacy, is at odds with the plain and ordinary meaning of “treat” and “treatment.”

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

CSPC argues claim construction on alternative grounds. For Grounds 1 and 2, CSPC 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 26-30. Under this construction, CSPC argues that the '552 patent's effective filing date is August 21, 2015. *Id.* at 36.

The verbiage of CSPC'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 CSPC's proposed construction.

The Board should moreover reject CSPC's proposed construction, because it conflicts with the '552 patent specification's description of the invention. A construction that 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. CSPC's construction, "attempting to cause a therapeutic improvement but not requiring actual efficacy," is inconsistent with the '552 patent's description of the invention. CSPC's construction is therefore inconsistent with the '552 patent's specification and should be rejected as such.

To the extent that CSPC cites portions of the specification allegedly supporting its construction, those portions are not definitional. CSPC 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 28 (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.

CSPC's other arguments ignore the intrinsic record. CSPC 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 28-29. In doing so, CSPC 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 CSPC 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 29 (emphasis in original). Instead, CSPC 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). CSPC is incorrect to suggest that the intrinsic record here is analogous to that of the cases it cites.

CSPC identifies no credible extrinsic evidence in support of its proposed construction. CSPC cites no technical dictionary definitions. To the extent that CSPC relies on its expert Dr. Ratain, his testimony is either duplicative of CSPC’s arguments or uninformed by the intrinsic record. Dr. Ratain, like CSPC, 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. CSPC’s Second Proposed Construction of “Treat” / “Treating”

For Ground 3, CSPC relies on an alternative, unspecified construction of “treat” and “treating” that would require “a showing of clinical efficacy.” Paper 1 at 36-37. CSPC otherwise fails to articulate what such a construction would entail. Under this alternative “construction,” CSPC argues that the effective filing date is no earlier than November 10, 2017. *Id.* at 36.

CSPC cites no support in the specification for its alternative “construction.” At most, CSPC suggests that the ’552 patent applicant’s arguments during prosecution compel a claim requirement of clinical efficacy. *See* Paper 1 at 35 (“[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 CSPC 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 CSPC 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”). CSPC’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. CSPC’s Petition Fails to Comply with Statutory Requirements

A. CSPC Fails to Identify All Real Parties-in-Interest

A petition for *inter partes* review may be considered “only if” it “identifies all real parties in interest.” 35 U.S.C. § 312(a)(2); *see also* 37 C.F.R. § 42.8(b)(1) (mandatory notices include identification of “each real party-in-interest for the party”). Determination of “whether a non-party is a ‘real party in interest’ demands a flexible approach that takes into account both equitable and practical considerations, with an eye toward determining whether the non-party is a clear beneficiary that has a pre-existing, established relationship with the petitioner.” *Applications in Internet Time, LLC v. RPX Corp.*, 897 F.3d 1336, 1351 (Fed. Cir. 2018); *see also* PTAB Consolidated Trial Practice Guide, 14 (Nov. 2019) (“[A]t a general level, the ‘real party-in-interest’ is the party that desires review of the patent.”); *id.* at 17-18 (stating that relevant factors include, *inter alia*, a non-party’s relationship with the petitioner and relationship to the petition itself).

CSPC's petition fails to identify all real parties-in-interest, because it fails to identify Cipla USA, Inc. ("Cipla"). CSPC's petition identifies three entities as real parties-in-interest: (1) CSPC Pharmaceutical Group Limited; (2) CSPC Ouyi Pharmaceutical Co., Ltd.; and (3) Conjupro Biotherapeutics, Inc. Paper 1 at 4. These three entities cooperated in the preparation and/or submission of NDA No. 218923, which seeks FDA approval to distribute, or have distributed an irinotecan liposome injection product (the "Proposed Conjupro Product") in the United States. Ex. 2020 (CSPC's Answer) at ¶¶ 15, 19, 20. Cipla also has an interest in the commercialization of the Proposed Conjupro Product by virtue of an exclusive license agreement with CSPC. See Ex. 2021 (CSPC Press Release). This relationship renders Cipla a real party-in-interest for purposes of CSPC's petition. CSPC's failure to identify Cipla as such runs afoul of statutory requirements.

B. CSPC's Non-Compliance with 37 C.F.R. § 42.63 Bars Reliance on the Conroy Protocol

All of CSPC's asserted grounds rely on the Conroy Protocol (Ex. 1004), which is written in a language other than English and for which CSPC has provided no certified translation. CSPC's failure to provide a certified translation of the Conroy Protocol violates 37 C.F.R. § 42.63, which governs the form of evidence in *inter partes* review proceedings. As set forth below, denial of CSPC's petition is justified on this ground alone.

Each of CSPC's asserted grounds of obviousness relies on the Conroy Protocol (Ex. 1004). Paper 1 at 39-63. Specifically, CSPC and its expert Dr. Ratain rely on the Conroy Protocol as disclosing a FOLFIRINOX regimen with a reduced dose of oxaliplatin, specifically at 60 mg/m². *See, e.g.*, Paper 1 at 33; Ex. 1002 at ¶¶ 104-106. The Conroy Protocol is a French language document, but Petitioners have not filed any certification attesting to the accuracy of the translation. The source document, the untranslated version, cannot be considered because CSPC has not even submitted it, it is in a language other than English, and the purported translation provided by CSPC is unaccompanied by a certificate of translation. *See* 37 C.F.R. § 42.63(b); Ex. 1004.

The Board has denied institution where, as here, each asserted ground of invalidity relies on a reference that fails to comply with 37 C.F.R. § 42.63(b). In *Zhongshan v. Nidec*, the Board denied institution where the petitioner failed to submit the required affidavit under § 42.63(b). *Zhongshan Broad Ocean Motor Co., Ltd. v. Nidec Motor Corp.*, IPR2014-01123, Paper 20 (PTAB Jan. 21, 2015). The Board held that “the filed copies of [foreign references] are defective because Petitioners failed to comply with 37 C.F.R. § 42.63(b) by omitting affidavits attesting to the accuracy of their translations. Accordingly, we do not consider these references, and as a result, we deny the Petition with respect to all asserted grounds because all such grounds rely on at least one of [foreign references].” *Id.*

at 7-8; *see also Shenzhen Aurora Tech. Co., Ltd. v. Putco, Inc.*, IPR2020-00670, Paper 10 at 5-6 (PTAB Aug. 27, 2020) (denying institution where the petitioner failed to submit the required affidavit under § 42.63(b) for two foreign prior-art references); *Shenzhen Kean Silicone Prod. Co., Ltd. v. PKOH NYC, LLC*, IPR2017-01327, Paper 14 at 42 (PTAB Dec. 6, 2017) (declining to institute on grounds based on foreign prior-art reference where petitioner failed to comply with § 42.63(b)). CSPC's failure to provide a certified translation for the Conroy Protocol likewise justifies dismissal of its petition.

At the very least, CSPC's failure to comply with 37 C.F.R. § 42.63 removes the Conroy Protocol from consideration as evidence. In *inter partes* review proceedings, § 42.63 governs the form of evidence. Material that fails to meet the requirements for evidence under the rules of § 42.63 is given no weight in the Board's decision whether to institute *inter partes* review. *See Bumble Bee Foods, LLC v. Kowalski*, IPR2014-00224, Paper 18 at 14-15 (PTAB June 5, 2014) (Board refused to rely on a declaration because it was not signed under penalty of perjury, thereby removing it from consideration because it failed to meet the requirements of evidence under § 42.63). To the extent that the Board does not deny CSPC's petition outright, the Conroy Protocol should be accorded no weight in this proceeding.

Indeed, CSPC’s purported translation of the Conroy Protocol contains apparent discrepancies and/or ambiguities that cast doubt on its accuracy. CSPC relies on the Conroy Protocol solely for its alleged disclosure of 60 mg/m² oxaliplatin. *See* Paper 1 at 16 (“Both the Conroy Protocol and the Conroy Appendix disclose that patients were to be given dose reduction of oxaliplatin from 85 mg/m² to 60 mg/m² based on various haematological toxicities, neutropenia, diarrhea, or any other grade 2 toxicities.” (citing Ex. 1004 at 16-18)). Yet, in the very section that CSPC cites as disclosing dose reduction of oxaliplatin, CSPC’s purported translation omits a symbol critical to understanding the supposed basis for such dose reduction:

Original (French)

Exhibit 1004

6.3.1 Toxicité hématologique

6.3.1.1 Selon le bilan biologique à J15

TRAITEMENT A : Folfirinox

NFS à J15	RETARD DE CYCLE	REDUCTION DE DOSE		
		Irinotecan (CPT-11)	Oxaliplatine (L-OHP)	LV5FU
PNN $\geq 1.5 \times 10^9/l$ et plaq $\geq 75 \times 10^9/l$	Pas de retard de cycle	Pas de réduction de dose		
PNN $< 1.5 \times 10^9/l$	Retarder le traitement jusqu'à J22 ou J29 si nécessaire). En cas de non récupération à J29, arrêt du traitement *	1 ^{er} épisode : réduction de dose à 150 mg/m ² 2 ^{ème} épisode : maintien de la dose à 150 mg/m ² 3 ^{ème} épisode : arrêt du traitement	1 ^{er} épisode : pas de réduction de dose 2 ^{ème} épisode : réduire la dose à 60 mg/m ² 3 ^{ème} épisode : arrêt du traitement	1 ^{er} épisode : supprimer le bolus de J1
Plaques $< 75 \times 10^9/l$	Retarder le traitement jusqu'à récupération (plaques $\geq 75 \times 10^9/l$). En cas de non récupération à J29, arrêt du traitement	1 ^{er} épisode : pas de réduction de dose 2 ^{ème} épisode : diminuer la dose à 150 mg/m ² 3 ^{ème} épisode : arrêt du traitement	1 ^{er} épisode : diminuer la dose du bolus et de la perfusion continue de 25% 2 ^{ème} épisode : maintien de la dose réduite 3 ^{ème} épisode : arrêt du traitement	1 ^{er} épisode : diminuer la dose du bolus et de la perfusion continue de 25%

* si pas de récupération après 2 retards de cure, arrêt du traitement sauf en cas de bénéfice clinique évident ; le cas sera alors discuté avec le coordinateur de l'étude et le promoteur.

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 $\geq 1.5 \times 10^9/L$ and platelets $\geq 75 \times 10^9/L$	No cycle delay	No dose reduction		
PNN $< 1.5 \times 10^9/L$	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/m ² 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/m ² 3 rd episode: discontinuation of treatment	1 st episode: eliminate bolus on D1
Platelets $< 75 \times 10^9/L$	Delay treatment until recovery (platelets $\geq 75 \times 10^9/L$). If no recovery at D29, discontinuation of treatment	1 st episode: no dose reduction 2 nd episode: reduce dose to 150 mg/m ² 3 rd episode: discontinuation of treatment	1 st episode: reduce dose to 60 mg/m ² 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.

Compare Ex. 2022 (Original Conroy Protocol) at 16 with Ex. 1004 at 16. CSPC’s purported translation of the Conroy Protocol also appears to reflect discrepancies and/or ambiguities in formulas for calculating oxaliplatin dose intensity:

Original (French)	Exhibit 1004
<p>7.6.1.3 Oxaliplatin (oxa) Les patients inscrits dans le bras A FOLFIRINOX auront reçu une dose de 85 mg/m² IV en perfusion de 2 heures à J1 avant toute autre perfusion toutes les 2 semaines.</p> <p>La durée de traitement par oxaliplatin (en semaines) au cours de l'étude est définie comme : $\text{[last dosing date - first dosing date + 14]} / 7$</p> <p>La dose intensité et la dose intensité relative par patient seront calculées pour des cycles de 2 semaines.</p> <p>La dose intensité (mg/m²/cycle) est définie comme :</p> $\frac{\text{Cumulative dose of Oxaliplatin (mg/m}^2\text{)}}{\text{Durée de traitement par oxaliplatin (en semaines)} / 2}$	<p>7.6.1.3 Oxaliplatin (oxa) Patients in the FOLFIRINOX arm (Arm A) will receive a dose of 85 mg/m² IV over 2 hours on Day 1, before any other infusion every 2 weeks.</p> <p>The treatment duration for oxaliplatin (in weeks) during the study is defined as: $\text{[last dosing date - first dosing date + 14]} / 7$</p> <p>Dose intensity and relative dose intensity per patient shall be calculated for 2-week cycles.</p> <p>Dose intensity (mg/m²/cycle) is defined as:</p> $\frac{\text{Cumulative dose of oxaliplatin (mg/m}^2\text{)}}{\text{Treatment duration with oxaliplatin (in weeks)} / 2}$ <p>AGREEMENT 11/0402 - CONFIDENTIAL -</p>

Compare Ex. 2022 (Original Conroy Protocol) at 86 with Ex. 1004 at 85-86.

Original (French)	Exhibit 1004
<p>La dose intensité relative est définie comme la dose intensité divisée par la dose prévue par cycle (85 mg/m²/2 semaines=cycle) i.e.</p> $\text{RDI} = \frac{\text{Dose Intensité}}{\text{Dose prévue}} = \frac{\frac{\text{Dose cumulée d'Oxaliplatin}}{\text{Durée de trt par oxaliplatin (sem)} / 2}}{\text{Dose prévue (mg/m}^2\text{/cycle)}}$	<p>Relative dose intensity is defined as the dose intensity divided by the expected dose per cycle (85 mg/m²/2 weeks = cycle), that is</p> $\text{RDI} = \frac{\text{Dose Intensity}}{\text{Planned dose}} = \frac{\frac{\text{Cumulative dose of oxaliplatin}}{\text{Treatment duration with oxaliplatin (weeks)} / 2}}{\text{Planned dose (mg/m}^2\text{/cycle)}}$

Compare Ex. 2022 (Original Conroy Protocol) at 86 with Ex. 1004 at 86.

These issues underscore the unreliability of CSPC's purported translation of the Conroy Protocol. If CSPC's petition is not denied outright on that basis, the Conroy Protocol should be entirely excluded from evidence in this proceeding.

C. CSPC Fails to Establish the Conroy Protocol and the Conroy Appendix Are Publicly Accessible Prior Art

CSPC fails to establish that the Conroy Protocol (Ex. 1004) and the Conroy Appendix (Ex. 1017) are proper bases for any decision to institute, let alone that they support an obviousness determination. As discussed *supra*, the Conroy Protocol is not evidence, because CSPC failed to comply with 37 C.F.R. § 42.63(b) by providing a certified translation. And, as discussed below, CSPC fails to

establish that either the Conroy Protocol or the Conroy Appendix is a prior-art printed publication.

It is well established that “the burden is on the petitioner to identify with particularity evidence sufficient to establish a reasonable likelihood that the reference was publicly accessible before the critical date of the challenged patent, and therefore that there is a reasonable likelihood that it qualifies as a printed publication.” *Hulu, LLC v. Sound View Innovations, LLC*, IPR2018-01039, Paper 29 at 13 (PTAB Dec. 20, 2019); *see also Symantec Corp. v. Trustees of Columbia Univ.*, IPR2015-00371, Paper 13 at 5, 9 (PTAB June 17, 2015) (denying institution where the petition failed to include discussion or cite to evidence sufficient to show that the asserted reference was a prior-art printed publication). Thus, CSPC bears the burden of establishing that the Conroy Protocol and the Conroy Appendix—references upon which CSPC relies for each of its asserted grounds of obviousness—qualify as prior art.

Whether a reference qualifies as a “printed publication” is a case-by-case inquiry into the facts and circumstances surrounding the reference’s disclosure to members of the public. *Acceleration Bay, LLC v. Activision Blizzard Inc.*, 908 F.3d 765, 772 (Fed. Cir. 2018). The key inquiry is whether the reference was made “sufficiently accessible to the public interested in the art” before the effective filing date. *In re Lister*, 583 F.3d 1307, 1311 (Fed. Cir. 2009) (citations omitted).

While indexing is not required to show that a work is publicly accessible, “some evidence that a person of ordinary skill could have reasonably found the website and then found the reference [(e.g., the specific webpage)] on that website is critical.” *Samsung Elecs. Co., Ltd. v. Infobridge Pte. Ltd.*, 929 F.3d 1363, 1369 (Fed. Cir. 2019). It is not sufficient that a webpage simply existed on the critical date. *See Acceleration Bay*, 908 F.3d at 772-74 (affirming Board decision that a reference uploaded to a website was not a prior-art printed publication).

Neither the Conroy Protocol nor the Conroy Appendix contains a publication date on its face. CSPC baldly asserts that each was “simultaneously published” with Conroy. *See* Paper 1 at 16 (“The authors of Conroy *simultaneously* published The Conroy Protocol (Ex. 1004) and The Conroy Appendix (Ex. 1017), to provide additional information about their work.” (emphasis added)). The only other information that CSPC identifies regarding the alleged publication dates of the Conroy Protocol and the Conroy Appendix is a statement in a *separate exhibit*—Conroy (Ex. 1003)—that “[t]he protocol, including the statistical analysis plan, is available with the full text of this article at NEJM.org.” *See* Paper 1, at 16 (quoting Ex. 1003 at 3). CSPC otherwise identifies nothing to establish that either the Conroy Protocol or the Conroy Appendix was publicly accessible as of the effective date, much less evidence that a POSA could have reasonably found the website and then found these references. Accordingly,

neither the Conroy Protocol nor the Conroy Appendix should be considered by the Board in its decision to institute.

Regardless, CSPC's attempted reliance on the Conroy Protocol and the Conroy Appendix is internally inconsistent and does not support obviousness of the claimed invention. CSPC argues that "the POSA reviewing the results of Conroy stating that the median dose intensity of oxaliplatin was 78% [of the standard 85 mg/m² dose] and the fact that the Conroy Protocol and the Conroy Appendix disclosed numerous dose reductions of oxaliplatin to 60 mg/m² oxaliplatin in the event of certain toxicity incidents, would have concluded that a significant portion of FOLFIRINOX patients were administered with 60 mg/m² oxaliplatin." Paper 1 at 41-42; *see also id.* at 16, 43, 47. But CSPC ignores that 78% of Conroy's 85 mg/m² oxaliplatin dose is *not* 60 mg/m² dose (instead, it is 66.3 mg/m²). CSPC does not even attempt to reconcile this discrepancy.

VIII. CSPC 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): CSPC's Asserted Combination Fails to Establish Obviousness

CSPC argues that it would have been obvious to modify FOLFIRINOX in order to arrive at the claimed combination therapy. These allegedly obvious modifications consist of four separate 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. In order to prevail in its obviousness challenge, CSPC has to show that, based on its assortment of asserted references, a POSA would have been motivated to make *all four* of these specific modifications together with a reasonable expectation of success in practicing the claimed methods. CSPC's obviousness argument fails for the reasons discussed below.

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

As set forth in Ipsen's discretionary denial brief, CSPC's petition entirely fails to explain why a POSA would have ignored other prior-art treatment options in favor of the multiple, specific modifications to FOLFIRINOX. CSPC, relying on Dr. Ratain, argues that a POSA would have been motivated to make a few specific modifications to a single chemotherapy regimen (FOLFIRINOX) in use at the time of invention. *See* Paper 1 at 41-43; Ex. 1002 at ¶¶ 231-264. But, as explained in Ipsen's discretionary denial brief and herein, CSPC and Dr. Ratain myopically ignore the existence of other treatment options and related considerations that weigh against such motivation.

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

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

The starting point for CSPC’s obviousness argument is the FOLFIRINOX regimen described in Conroy. As CSPC describes, FOLFIRINOX was the established, “gold standard” of care in treating metastatic pancreatic cancer at the time of the invention. *See* Paper 1 at 1 (“[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)), 3 (stating that FOLFIRINOX was “considered the gold standard at the time”), 7 (“At the time of the filing of the patent, the ‘gold standard’ of first-line treatment of patients with metastatic pancreatic cancer was FOLFIRINOX.”); *see also id.* at 16,

32, 34-35, 41, 43, 47, 61 (referring to FOLFIRINOX as a “gold standard,” “established gold-standard,” or “gold-standard first-line” regimen or therapy).

Dr. Ratain and CSPC’s own cited references similarly characterize FOLFIRINOX as the “gold standard” of care. 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 moreover reflected in CSPC’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 CSPC’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.

CSPC identifies no motivation to depart from FOLFIRINOX’s established “gold standard” of care, much less in the multiple, specific ways that would have been necessary in order to arrive at the claimed invention. CSPC suggests that concerns over toxicity of the FOLFIRINOX regimen would have prompted a POSA to modify FOLFIRINOX. *See* Paper 1 at 2. As discussed *supra*, in order to arrive at the ’552 patent’s claimed treatment regimen, such concerns would have had to motivate a POSA to make four specific modifications to FOLFIRINOX.

But CSPC fails to establish that toxicity concerns would have prompted a POSA to make the combination of *all four* of these allegedly obvious modifications at once.

As an initial matter, CSPC and Dr. Ratain take the dose-modification disclosures of Conroy, the Conroy Protocol, and the Conroy Appendix out of context. CSPC and Dr. Ratain cite Conroy's reference to the "median dose intensity" for the various FOLFIRINOX components. *See* Paper 1 at 41-42; Ex. 1002 at ¶ 69. But neither CSPC 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 CSPC 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 CSPC 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 CSPC argues—chemotherapy drug components of FOLFIRINOX.

A POSA would not have understood Conroy, the Conroy Protocol, or the Conroy Appendix to teach—as CSPC suggests—a first-line combination treatment that includes, *ab initio*, a 60 mg/m² dose of oxaliplatin. CSPC 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. 2004 (Marsh) at 1, 3 (Table 2). A POSA would not have been motivated, based on CSPC’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. CSPC 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. CSPC 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 CSPC 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 CSPC 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, CSPC identifies no legitimate motivation for a POSA to introduce liposomal irinotecan to the FOLFIRINOX regimen. CSPC suggests that FOLFIRINOX’s “gold-standard” status would have supplied such motivation. *See* Paper 1 at 32 (“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 Bayever’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)). Indeed, neither CSPC 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.

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. CSPC 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 1-2. 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 ¶ 73.¹ 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

¹ CSPC and Dr. Ratain ignore that the ’552 patent’s claimed combination therapy differs from FOLFIRINOX in both its constituent components and their dosages.

that issue in Ipsen's favor. Nevertheless, CSPC cites Bayever's disclosure of properties of liposomal irinotecan in support of obviousness. *See, e.g.*, Paper 1 at 2. But apart from toxicity concerns, CSPC fails to identify any problem that would have motivated a POSA to turn to liposomal irinotecan on the basis of these properties, let alone in combination with the other recited components of the invention. That the claimed combination was later found to provide a benefit over other therapies cannot suffice as requisite motivation. *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 CSPC 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 CSPC 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, CSPC and Dr. Ratain rely on the disclosure of Bayever for use of liposomal irinotecan, generally. *See* Paper 1 at 42; Ex. 1002 at ¶¶ 235-240. But neither CSPC 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. CSPC

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 42; 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”). CSPC 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. CSPC Does Not Articulate Any Reasonable Expectation of Success in Practicing the Claimed Invention

Even if CSPC presented a coherent motivation to modify FOLFIRINOX in the multiple, specific ways that it alleges would have been obvious (it does not), CSPC entirely fails to articulate a reasonable expectation of success in doing so. That is, CSPC articulates no basis to conclude that a POSA would reasonably expect the allegedly obvious modifications to result in an antineoplastic therapy as claimed. At most, CSPC 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 46-49.

Neither argument is availing.

(a) CSPC's "Result-Effective Variable" Argument Has Already Been Considered and Is Unavailing

CSPC 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 46-47. This argument lacks merit for several reasons.

First, and as discussed in Ipsen's discretionary denial brief, there is no question that the Patent Office has already considered this argument and decided in favor of patentability. Indeed, CSPC explicitly acknowledges that the '552 patent applicant overcame this argument during prosecution. See Paper 1 at 46 ("[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, and as also discussed in Ipsen's discretionary denial brief, CSPC 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. CSPC 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 16. But 78% of 85 mg/m² is 66.3 mg/m², not the claimed 60 mg/m². Neither CSPC nor Dr. Ratain attempts to address this discrepancy. To the extent Conroy informs what would have constituted "routine experimentation" of a result-effective variable, it would not lead a POSA to the claimed dosage of oxaliplatin.

Third, CSPC'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. CSPC'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.

CSPC’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. 2023 (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. 2024 (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. 2025 (Ratain 2014) at 1. Literature also recognizes inter-patient variability associated with 5-FU. *See, e.g.*, Ex. 2026 (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. 2027 (Gurney 2002) 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. 2028), 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. 2028 (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. 2026 (Bach) at 1 (“[T]he routine use of combination therapy in oncology patients makes establishing relationships between drug concentration and therapeutic end points difficult.”). Thus, inter-patient variability in response to single-drug chemotherapy regimens are further unpredictable in the context of combination chemotherapy regimens.

CSPC’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.

Other references cited by CSPC 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 CSPC 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/m ² 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 CSPC'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. 2008 (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. 2009 (Thota) at 4 (“The failure rate of phase III clinical trials in advanced pancreatic cancer is high (87%).”); Ex. 2008 (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 CSPC 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. CSPC 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 42-43. 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. CSPC also cites Ko (Ex. 1008), which summarizes preclinical study results and describes the results of a Phase 2 study of the three-drug combination described in Bayever. Ex. 1008 at 2-5. Finally, CSPC cites Kim (Ex. 1058) and Hann (Ex. 1059), which describe the results of preclinical studies conducted in animals. *See* Ex. 1058, Ex. 1059. CSPC relies on Dr. Ratain for the predictive value of such data. *See* Paper 1 at 47 (“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.”). CSPC’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 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. 2010 (Ratain 2005) at 1 (emphasis added); *see also* Ex. 2007

(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 CSPC 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, unexpected results properly support non-obviousness of the claimed methods. CSPC’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 33-35. CSPC’s critiques fail.

CSPC mischaracterizes the ’552 patent applicant’s statements relating to unexpected results made during prosecution. Specifically, CSPC 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 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, CSPC reargues issues that have already been before the Patent Office and decided in Ipsen’s favor.

To the extent that CSPC suggests that post-filing evidence of unexpected results cannot support patentability, that is incorrect. CSPC makes repeated reference to the “post-filing” evidence of unexpected results submitted during prosecution. Paper 1 at 33, 34, 50. 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.

CSPC attempts but fails to refute the ’552 patent applicant’s evidence of unexpected results. In attempting to do so, CSPC 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 34-35 (emphasis in original); *see also id.* at 51-52. But as discussed in Ipsen’s discretionary denial brief, these references amount to cross-trial comparisons that CSPC itself argues are inherently unreliable. *See* Paper 1 at 34.

Regardless, neither of CSPC’s cited references even purport to establish—as CSPC argues—that NALIRIFOX has “identical efficacy” to FOLFIRINOX. Nichetti reflects a review and meta-analysis, “with all the inevitable limitations” inherent to such a study, of data from a number of different clinical trials involving different regimens for treatment of pancreatic cancer. *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 CSPC 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. 2029 (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. 2030 (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. 2031 (Cockrum). This suggests, directly contrary to CSPC'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. 2032 (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. 2033 (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. 2034 (Kobayashi) at 1 (concluding that “GnP is recommended as the first-line treatment for [patients] with [metastatic pancreatic cancer] compared to mFOLFIRINOX”); Ex. 2035 (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. 2033 (Skorupan) at 3. These recent developments contradict CSPC’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 CSPC’s Collection of References from Ground 1, Do Not Establish Obviousness

CSPC 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 58-59. As CSPC concedes, none of these references discloses—as

claimed—that oxaliplatin is administered 2 hours after liposomal irinotecan. *Id.* at 59. Its cited references suffer from additional deficiencies, as discussed below.

As an initial matter, CSPC 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 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. CSPC does not even attempt to address this discrepancy.

Bayever does not support CSPC’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. CSPC relies on Bayever’s alleged disclosure that “liposomal irinotecan MM-398 should be administered first before any other drugs.” Paper 1 at 58. The only citation to Bayever that CSPC 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 CSPC’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. CSPC 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 58-59. 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 CSPC’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.

CSPC 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 59. CSPC 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.* CSPC’s arguments fail for the same reasons discussed with respect to claims 1 and 2.

None of CSPC’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.

CSPC 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. CSPC 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 60. CSPC 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. CSPC’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 CSPC’s Other Asserted References

CSPC 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 CSPC's arguments fail for the reasons discussed with respect to Grounds 1 and 2. Regardless, CSPC's arguments based on Carnevale and Dean also fail for the reasons discussed below.

The underlying assumption for CSPC'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 reasons set forth herein, CSPC’s petition should be denied. As discussed in greater detail in Ipsen’s discretionary denial brief, CSPC merely restates the same obviousness arguments, based on the same lead references, that the ’552 patent applicant has already overcome. CSPC fails to meet its burden to show that either the Conroy Protocol or the Conroy Appendix—upon which it relies for each of its asserted grounds—qualify as prior art. CSPC’s obviousness argument fails as a substantive matter, for at least the reason that it begins and ends with FOLFIRINOX. To the extent that CSPC articulates a reason that a POSA would depart from FOLFRINOX—the “gold standard” at the time—it is to address toxicity concerns. But the prior art, including references relied upon by CSPC and its expert, describes solutions to that problem that do not lead to the ’552 patent’s

invention. CSPC fails to identify a reasonable likelihood that it will prevail, and the Board should decline to institute proceedings accordingly.

Date: May 23, 2025

By: /s/ James Glass

James M. Glass (Reg. No. 46,729)
QUINN EMANUEL URQUHART &
SULLIVAN LLP
295 5th Ave.
New York, New York 10016
Email: jimglass@quinnemanuel.com
Phone: 212-849-7142
Fax: 212-849-7100

Counsel for Patent Owner

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 12,811 words and thus complies with the applicable word limit.

Date: May 23, 2025

By: /s/ James Glass

James M. Glass (Reg. No. 46,729)
QUINN EMANUEL URQUHART &
SULLIVAN LLP
295 5th Ave.
New York, New York 10016
Email: jimglass@quinnemanuel.com
Phone: 212-849-7142
Fax: 212-849-7100

Counsel for Patent Owner.

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

The undersigned hereby certifies that on May 23, 2025 copies of the foregoing document and supporting exhibits were served upon the following parties via electronic mail, with a copy to ipdocket@foxrothschild.com (referencing Attorney Docket No. 340008.00021):

Lead Counsel:

Luke Toft (Reg. No. 75,311)
ltoft@foxrothschild.com
Fox Rothschild LLP
33 South 6th Street, Suite 3600
Minneapolis, MN 55402
Tel: (612) 607-7336
Fax: (612) 607-7100

Backup Counsel:

Joe Chen (Reg. No. 70,066)
joechen@foxrothschild.com
Fox Rothschild LLP
212 Carnegie Center, Suite 400
Princeton, NJ 08540
Tel: (609) 844-3024
Fax: (609) 896-1469

Howard S. Suh (pro hac vice to be filed)
hsuh@foxrothschild.com
Fox Rothschild LLP
101 Park Avenue, 17th Floor
New York, NY 10178
Tel: (212) 878-7914
Fax: (212) 692-0940

Date: May 23, 2025

By: /s/ James Glass

James M. Glass (Reg. No. 46,729)
QUINN EMANUEL URQUHART &
SULLIVAN LLP
295 5th Ave.
New York, New York 10016
Email: jimglass@quinnemanuel.com
Phone: 212-849-7142
Fax: 212-849-7100

Counsel for Patent Owner