

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 REQUEST FOR
DISCRETIONARY DENIAL OF INSTITUTION**

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LIST OF EXHIBITS

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Ex. 2001	File History of U.S. Patent No. 11,344,552, March 6, 2018 Notice of References Cited (“March 6, 2018 Notice”)
Ex. 2002	File History of U.S. Patent No. 11,344,552, July 8, 2019 Information Disclosure Statement by Applicant (“July 8, 2019 IDS”)
Ex. 2003	File History of U.S. Patent No. 11,344,552, August 26, 2021 Information Disclosure Statement by Applicant (“August 26, 2021 IDS”)
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”)
Ex. 2005	Somala Mohammed et al., <i>Pancreatic cancer: Advances in treatment</i> , 20(28) World J. Gastroenterol 9354 (2014) (“Mohammed”)
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. 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. 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. 2010	Mark J. Ratain, <i>Phase II Oncology Trials: Let’s Be Positive</i> , 11(16) Clin. Cancer Rsch. 5561 (2005) (“Ratain 2005”)
Ex. 2011	Eastern Research Group, Inc., <i>Examination of Clinical Trial Costs and Barriers for Drug Development</i> (2014) (“ERG 2014”)
Ex. 2012	Ramaswamy Govindan, <i>Phase III failure rates in oncology drugs unacceptable</i> , 16(8) Oncology News Int’l (2007) (“Govindan”)

Exhibit	Description
Ex. 2013	Anneke T. Schroen et al., <i>Preliminary evaluation of factors associated with premature trial closure and feasibility of accrual benchmarks in phase III oncology trials</i> , 7 Clin. Trials 312 (2010) (“Schroen”)

I. INTRODUCTION

Pursuant to the Director’s March 26, 2025 Memorandum Regarding Interim Processes for PTAB Workload Management (“March 26, 2025 Memorandum”), Patent Owner Ipsen Biopharm Ltd. (“Ipsen”) files this Request for Discretionary Denial of 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, denial of CSPC’s petition is warranted on several grounds.

First, CSPC presents the same arguments, based on the same or substantially the same references, that the Patent Office has already considered. CSPC’s sole validity challenge is on the basis of alleged obviousness. And CSPC bases its obviousness challenge on the same lead references—Ex. 1003, Conroy and Ex. 1006, Bayever—that were the basis for obviousness arguments overcome during prosecution of the ’552 patent. The Patent Office has therefore considered whether this particular combination of references—each of which discloses a different combination therapy, composed of different chemotherapy drugs, in different doses from the claimed regimen—renders the ’552 patent claims obvious. After such consideration, the Patent Office allowed the ’552 patent claims, and CSPC fails to

identify any material error by the Patent Office in doing so. Denial is therefore warranted under 35 U.S.C. § 325(d).

Second, CSPC's obviousness argument suffers from weaknesses that further favor denial. Specifically, CSPC and its expert, Dr. Ratain, present obviousness arguments that impermissibly rely on hindsight and overlook critical discrepancies between the asserted prior art and the '552 patent claims. These deficiencies even further support denial.

Finally, the settled expectations of Ipsen, in bringing a novel treatment to patients who suffer from an incurable disease with an extremely grim prognosis (median survival after diagnosis is less than one year, with a 2% five-year survival rate), also merit consideration. Ipsen's investment and contribution in this therapeutic area—where the cost and complexities associated with clinical research are high, and the likelihood of success is low—further favors denial of CSPC's petition.

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%.

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, following the Patent Office’s determination of patentability over, *inter alia*, Conroy (Ex. 1003) and Bayever (Ex. 1006). Each of these references discloses a different combination therapy for the treatment of metastatic pancreatic cancer, and the therapies disclosed in each differ from that of the ’552 patent’s claimed methods as summarized below:

Conroy (“FOLFIRINOX”)	Bayever	’552 Patent (“NALIRIFOX”)
180 mg/m ² non-liposomal irinotecan	60 or 80 mg/m ² liposomal irinotecan	60 mg/m ² liposomal irinotecan
85 mg/m ² oxaliplatin		60 mg/m ² oxaliplatin
400 mg/m ² bolus, followed by 2,400 mg/m ² infusion of 5-fluorouracil	2,400 mg/m ² infusion of 5-fluorouracil	2,400 mg/m ² of 5- fluorouracil
400 mg/m ² leucovorin	200 mg/m ² (<i>l</i> -form) or 400 mg/m ² (<i>l</i> + <i>d</i> racemic form)	200 mg/m ² of <i>l</i> -form of leucovorin or 400 mg/m ² of racemic (<i>l</i> + <i>d</i>) form of leucovorin

Ex. 1003 (Conroy) at 3; Ex. 1006 (Bayever) at 32-34 (Arm C); Ex. 1001 (’552 patent) at claims 1, 12.

Conroy’s FOLFIRINOX regimen differs from the ’552 patent’s combination therapy in several respects. For example, the FOLFIRINOX regimen includes

non-liposomal irinotecan (also referred to as “free irinotecan” or “irinotecan”), in a different dosage, from the ’552 patent regimen’s liposomal irinotecan (also referred to as “MM-398,” “PEP02,” or “nal-IRI”). *See* Ex. 1003 (Conroy) at 3. The FOLFIRINOX regimen also includes a higher dosage of both oxaliplatin and 5-fluorouracil (also referred to as “fluorouracil,” “FU,” or “5-FU”). *Id.*

Bayever’s regimen likewise differs from the ’552 patent’s combination therapy. Unlike the ’552 patent’s claimed methods, the Bayever regimen does not include oxaliplatin at all, in any dose. *See* Ex. 1006 (Bayever) at 32-34 (Arm C). In addition, the regimen disclosed in Bayever was administered as second-line therapy, to patients who had progressed on prior gemcitabine therapy, not as a first-line treatment. Ex. 1006 (Bayever) at 26.

The Patent Office found that the ’552 patent’s NALIRIFOX regimen is non-obvious over the combination of Conroy (Ex. 1003) and Bayever (Ex. 1006). Conroy and Bayever were the basis for a number of obviousness rejections throughout prosecution. Ex. 1084 at 190-201 (Mar. 6, 2018 Rejection); *id.* at 314-327 (Sept. 11, 2018 Rejection); Ex. 1088 at 57-69 (July 8, 2019 Rejection); Ex. 1097 at 188-203 (Feb. 27, 2020 Rejection); Ex. 1119 at 9-22 (Aug. 26, 2021 Rejection). In each rejection, the Patent Office submitted that—notwithstanding the differences between and among them—a POSA would have nonetheless been motivated to combine the disclosures of Conroy and Bayever in order to arrive at

the '552 patent's claimed combination therapy with a reasonable expectation of success. *See, e.g.*, Ex. 1084 (Mar. 6, 2018 Rejection) at 193-94. The '552 patent applicant ultimately overcame these rejections, and the '552 patent issued on May 31, 2022. *See* Ex. 1123 at 401-402 (Notice of Allowability); Ex. 1123 at 461-465 (Corrected Notice of Allowability); Ex. 1001 at 1.

III. THE BOARD SHOULD EXERCISE DISCRETIONARY DENIAL

CSPC repeats the same obviousness arguments, based on the same lead references, that the Patent Office already considered during prosecution of the '552 patent. There are other compelling reasons to deny CSPC's petition, such as the unlikelihood that CSPC will prevail in its challenge, and rewarding Ipsen's innovative contributions to the field of pancreatic cancer treatment, that justify denial. Together, all of these grounds support discretionary denial.

A. The Board Should Exercise Denial Under 35 U.S.C. § 325(d)

The Board may reject a petition where “the same or substantially the same prior art or arguments previously were presented to the Office.” 35 U.S.C. § 325(d). In deciding whether to do so, the Board undertakes a two-part analysis that considers: (1) whether the same or substantially the same art or arguments were previously presented to the Patent Office; and (2) if either part of (1) is satisfied, whether petitioner has demonstrated that the Patent Office erred in a manner material to patentability. *Advanced Bionics, LLC v. MED-EL*

Elektromedizinische Geräte GmbH, IPR2019-01469, Paper 6 at 7-8 (PTAB Feb. 13, 2020) (precedential).

Whether denial under 35 U.S.C. § 325(d) is warranted entails a fact-specific inquiry that takes into account:

- (a) the similarities and material differences between the asserted art and the prior art involved during examination;
- (b) the cumulative nature of the asserted art and the prior art evaluated during examination;
- (c) the extent to which the asserted art was evaluated during examination, including whether the prior art was the basis for rejection;
- (d) the extent of the overlap between the arguments made during examination and the manner in which Petitioner relies on the prior art or Patent Owner distinguishes the prior art;
- (e) whether Petitioner has pointed out sufficiently how the Examiner erred in its evaluation of the asserted prior art; and
- (f) the extent to which additional evidence and facts presented in the Petition warrant reconsideration of the prior art or arguments.

Becton, Dickinson & Co. v. B. Braun Melsungen AG, IPR2017-01586, Paper 8 at 17-18 (PTAB Dec. 15, 2017) (precedential as to § III.C.5, first paragraph); *see also* Patent Trial and Appeal Board Consolidated Trial Practice Guide, 62-63 (Nov. 2019).

As detailed below, CSPC relies on the same two lead references that were the basis for multiple obviousness rejections and were therefore discussed

extensively during prosecution. Any allegedly “new” references identified by CSPC in its petition are cumulative at best. CSPC’s attempt to identify material error in the Patent Office’s determination of patentability is flawed, because it relies on mischaracterization of the ’552 patent applicant’s arguments and/or the relevant legal standard. Together, these factors favor the Board’s exercise of discretionary denial.

1. CSPC Presents the Same or Substantially the Same Prior Art and Arguments That Were Overcome Before the Patent Office

CSPC bases its obviousness argument on what it describes as the “already established gold-standard FOLFIRINOX regimen” for treating metastatic pancreatic cancer. *See, e.g.*, Paper 1 at 41. According to CSPC, it would have been obvious to modify FOLFIRINOX in a number of different ways, namely by: (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. As discussed below, the Patent Office has already considered and rejected the alleged obviousness of these modifications.

(a) The Patent Office Has Already Considered CSPC's Allegedly Obvious Modification of FOLFIRINOX to Include Liposomal Irinotecan

The Patent Office is well aware of CSPC's lead reference, Conroy, and its disclosure of the FOLFIRINOX treatment regimen. The Patent Office repeatedly cited Conroy and FOLFIRINOX as a basis for rejections under 35 U.S.C. § 103 throughout the prosecution of the '552 patent. *See, e.g.*, Ex. 1084 at 193 (“Conroy disclosed FOLFIRINOX (oxaliplatin; irinotecan; leucovorin and fluorouracil) treatment of patients having metastatic pancreatic cancer.”); *id.* at 317; Ex. 1088 at 60; Ex. 1097 at 191; Ex. 1119 at 12; Ex. 2001 (March 6, 2018 Notice) at 1. Thus, the Patent Office has already considered whether the claimed methods are obvious in view of the FOLFIRINOX regimen disclosed in Conroy.

The Patent Office is also well aware of Bayever, CSPC's other lead reference. As with Conroy, the Patent Office repeatedly cited Bayever as a basis for rejections under 35 U.S.C. § 103 throughout the prosecution of the '552 patent. *See, e.g.*, Ex. 1084 at 192-193 (“Bayever et al [sic] disclosed a method for treatment of pancreatic cancer in a patient (e.g., a human, at page 3, 1st paragraph), comprising co-administering to the patient active agents, at a dose of 60 mg/m² (e.g., liposomal irinotecan); *see also* Ex. 2001 (March 6, 2018 Notice) at 1. Bayever further disclosed 5-fluorouracil at a dose of 2400 mg/m² and leucovorin (*l* form administered at 200 mg/m² or the l+d racemic form administered at 400

mg/m²).”); *id.* at 316-317; Ex. 1088 at 59-60; Ex. 1097 at 190-191; Ex. 1119 at 11. Thus, CSPC’s two lead references—Conroy and Bayever—were extensively discussed during prosecution of the ’552 patent.

CSPC argues obviousness based on Conroy’s disclosure of FOLFIRINOX in view of Bayever. According to CSPC, a POSA would have been motivated to replace “free-irinotecan” in FOLFIRINOX with “liposomal irinotecan in view of Bayever, which by then had already disclosed a method of treating metastatic pancreatic cancer with the same liposomal irinotecan composition of the Challenged Claims along with the exact same claimed doses of leucovorin and 5-FU.” Paper 1 at 42.

The Patent Office considered whether the combination of Conroy and Bayever render the ’552 patent claims obvious and resolved that issue in Ipsen’s favor. As discussed, the Patent Office repeatedly cited Conroy and Bayever as lead references in obviousness-based rejections throughout prosecution. In doing so, the Patent Office specifically and repeatedly noted that Bayever discloses liposomal irinotecan but not oxaliplatin and that Conroy discloses oxaliplatin but not liposomal irinotecan. *See* Ex. 1084 at 192-193; *id.* at 316-317; Ex. 1088 at 59-60; Ex. 1097 at 190-191; Ex. 1119 at 11-12. Thus, the Patent Office has already considered the alleged obviousness of combining Conroy and Bayever.

CSPC's reliance on Bayever, Saif, and Ko to support the alleged obviousness of using liposomal irinotecan in FOLFIRINOX is cumulative, adding nothing new. CSPC cites Bayever, Saif, and Ko for the proposition that a POSA would have been motivated to replace the free irinotecan used in the FOLFIRINOX with liposomal irinotecan. *See* Paper 1 at 42. With respect to Bayever, CSPC and its expert specifically rely on Bayever's disclosure of properties of liposomal irinotecan and its application as second-line therapy for metastatic pancreatic cancer, along with 5-FU and leucovorin. *Id.*; Ex. 1002 ¶¶ 235-40. CSPC cites Ko and Saif for the proposition that a POSA would have evaluated the potential use of liposomal irinotecan as first-line therapy and would have made that substitution to the FOLFIRINOX regimen accordingly. *See* Paper 1 at 41-42.

Ko was before the Patent Office during prosecution. *See, e.g.*, Ex. 1088 at 75 (No. 32); Ex. 1091 at 323 (No. 3); Ex. 1118 at 199 (No. 18); *id.* at 349-354 (containing Ex. 1008 in full); Ex. 2002 (July 8, 2019 IDS) at 4; Ex. 2003 (August 26, 2021 IDS) at 27. Ko purports to describe the results of a Phase II study of liposomal irinotecan as second-line monotherapy for patients with metastatic pancreatic cancer. *See* Ex. 1008 (Ko) at 2. The Phase II study described in Ko was also before the Patent Office during prosecution. *See* Ex. 1091 at 272 (Nos. 16-18); Ex. 1084 at 532-534 (containing the study record for NCT00813163). Ko

reports the administration of 120 mg/m² liposomal irinotecan every three weeks as monotherapy in patients with metastatic pancreatic cancer who had failed gemcitabine-based chemotherapy. Ex. 1008 (Ko) at 2. Ko reports that liposomal irinotecan as monotherapy exhibited anti-tumor activity and was generally well-tolerated in most patients, although cautions of its use in such a “fragile patient population.” *Id.* at 5.

Ko does not, as CSPC argues, provide motivation to substitute liposomal irinotecan for irinotecan in FOLFIRINOX. To the extent that Ko discloses therapeutic utility of liposomal irinotecan, such disclosure relates to liposomal irinotecan as monotherapy and in a different dose than used in the ’552 patent’s claimed combination therapy. *Compare id.* at 2 (disclosing 120 mg/m² liposomal irinotecan every three weeks) *with* Ex. 1001 at claim 1 (reciting 60 mg/m² of liposomal irinotecan “once every two weeks”). CSPC’s selective quotation of Ko is moreover misleading. *See* Paper 1 at 42. Far from suggesting that liposomal irinotecan “should be explored” in FOLFIRINOX, the referenced passage states:

[G]iven the emergence of FOLFIRINOX as a front-line standard in patients with good performance status, the utility of [liposomal irinotecan] in irinotecan-pretreated patients, alone or in combination with gemcitabine, also merits further investigation.

Ex. 1008 at 5. At most, the authors suggest further investigation of liposomal irinotecan as second-line therapy, *alone* or in *combination with gemcitabine*—not in the FOLFIRINOX regimen, let alone the claimed first-line regimen.

Saif purports to describe the results of NAPOLI 1, a study that the Patent Office considered during prosecution. The “NAPOLI 1” study evaluated the combination therapy of liposomal irinotecan, 5-fluorouracil, and leucovorin (versus 5-fluorouracil and leucovorin) as second-line treatment in patients with gemcitabine-refractory metastatic pancreatic cancer. Ex. 1007 (Saif) at 1.

The NAPOLI 1 study was before the Patent Office during prosecution. *See* Ex. 1097 at 213 (Nos. 25 and 26, referring to “Clinical Trials Identifier NCT01494506”). Publications discussing the NAPOLI 1 study and its results were also before the Patent Office. *See, e.g.*, Ex. 1084 at 407 (No. 38, Von Hoff et al., “NAPOLI 1: Randomized Phase 3 Study of MM-398 (nal-IRI), With or Without 5-Fluorouracil and Leucovorin, Versus 5-Fluorouracil and Leucovorin, in Metastatic Pancreatic Cancer Progressed on or Following Gemcitabine-Based Therapy.”); Ex. 1085 at 218-227 (Von Hoff presentation); Ex. 1088 at 82 (No. 12, Wang-Gillam et al., “Nanoliposomal Irinotecan with Fluorouracil and Folinic Acid in Metastatic Pancreatic Cancer After Previous Gemcitabine-Based Therapy (NAPOLI-1): A Global, Randomised, Open-Label, Phase 3 Trial”); Ex. 1090 at

153-165 (Wang-Gillam publication). Saif's disclosure of the NAPOLI 1 study results is therefore cumulative of art that the Patent Office considered.

Regardless, the NAPOLI 1 study results reported in Saif relate to a combination therapy different from FOLFIRINOX and the '552 patent's claimed methods. Unlike FOLFIRINOX and the '552 patent's methods, the treatment regimen of NAPOLI 1 does not include oxaliplatin, in any dosage. Thus, Saif discloses no more than and is, at best, cumulative of references that the Patent Office already considered.

CSPC relies on a selective and misleading quotation of Saif to suggest that it provides motivation to modify FOLFIRINOX by including liposomal irinotecan in place of non-liposomal irinotecan. *See* Paper 1 at 42-43 ("Saif goes even further: first by asking that '[n]ow that we have . . . FOLFIRINOX as an option for first-line treatment, how will this [MM-398] regimen fit in the algorithm of treatment,' and then answering '[i]t [sic] seems logical to test this [MM-398] drug/regimen further' to determine 'replacing irinotecan in FOLFIRINOX with MM-398.'"). Read in context, Saif suggests no such thing.

At most, Saif states that the NAPOLI 1 study results "bring[] new questions." Ex. 1007 (Saif) at 1. What immediately follows are three separate questions, none of which has an answer, much less the question-and-answer that CSPC misleadingly suggests. *See id.* One unanswered question is "how will [the

NAPOLI 1 regimen] fit in the algorithm of the treatment?” *Id.* Separately, another unanswered question is “***will it be worth*** replacing irinotecan in FOLFIRINOX with MM-398,” given concerns of bone marrow toxicity. *Id.* (emphasis added). At most, Saif raises questions about the future of metastatic pancreatic cancer treatment. Such speculation does not, as CSPC misleadingly argues, evince a direct suggestion to replace irinotecan in FOLFIRINOX with liposomal irinotecan, let alone additionally decreasing the dose of oxaliplatin to 60 mg/m² and removing the bolus of 5-fluorouracil, and doing so with a reasonable expectation of success. To the contrary, Saif questions whether one particular modification would be “worth it,” particularly given toxicity issues that might result.

(b) The Patent Office Has Already Considered CSPC’s Allegedly Obvious Modification of FOLFIRINOX to Reduce the Dose of Oxaliplatin

In addition to the allegedly obvious substitution of liposomal irinotecan, CSPC argues that it would have been obvious to reduce the dose of oxaliplatin in FOLFIRINOX, from 85 mg/m² to 60 mg/m². *See* Paper 1 at 46-47. CSPC argues that “adjusting the dose of oxaliplatin was a result effective variable subject to routine optimization” is “***a critical point not appreciated by the Examiner or Patent Owner during prosecution.***” Paper 1 at 47 (emphasis in original). CSPC’s argument that the Patent Office did not consider this issue is irreconcilable with CSPC’s statements elsewhere in its petition, as well as the file history.

CSPC states that the Patent 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.” Paper 1 at 46. Indeed, the Patent Office explicitly based several obviousness rejections on the argument that oxaliplatin dosage is a result-effective variable that could be optimized by routine experimentation. A September 11, 2018 rejection states:

[O]xaliplatin, and its amount, is recognized to have different effects (greater or less toxicity, as taught by Alcindor and discussed above) with changing amounts used. Thus, the general condition (the dosage) is known and the amount of this ingredient is recognized to be ***result effective***.

Ex. 1084 at 318 (emphasis added). The Patent Office repeated this argument in subsequent rejections, on the basis of another reference (Melis):

[O]xaliplatin [sic], and its amount, is recognized to have different effects (treatment of advanced pancreatic adenocarcinoma) with changing amounts used. Thus, the general condition (the dosage) is known and the amount of this ingredient is recognized to be ***result effective***. Therefore, result effective variables can be optimized by routine experimentation, and it would have been prima facie obvious to optimize the dosage of the oxaliplatin present in the combined composition of Bayever and Conroy, as taught by Melis.

Ex. 1088 at 61 (emphasis added); *see also* Ex. 1097 at 192 (same argument); Ex. 1119 at 12-13 (same argument). Thus, the Patent Office has already resolved the

issue of whether oxaliplatin (and its dosage) is a result-effective variable subject to routine experimentation in Ipsen's favor.

CSPC argues nothing new in its petition. CSPC cites Cantore, as opposed to Melis (cited during prosecution), for the alleged obviousness of oxaliplatin dose reduction. *See* Paper 1 at 32-33. But Cantore does not address the deficiencies of Melis; moreover, Cantore was before the Patent Office during prosecution. *See, e.g.,* Ex. 1088 at 89 (No. 7); Ex. 2002 (July 8, 2019 IDS) at 14. Thus, Cantore is not a new reference.

Nevertheless, a POSA would not be motivated, based on Cantore, to arrive at the claimed combination regimen. To the extent that Cantore discusses oxaliplatin, it teaches away from dose reduction. Cantore states that, “[i]n light of the excellent tolerability of this regimen, dosages could possibly be *increased* in future studies in an effort to boost response.” Ex. 1009 (Cantore) at 4 (emphasis added). The authors conclude: “[f]uture studies should try *higher doses* of irinotecan and oxaliplatin in such patients.” *Id.* at 5. If anything, Cantore teaches an increase, not a reduction, in the dose of oxaliplatin.

**(c) The Patent Office Has Already Considered CSPC's
Allegedly Obvious Modification of FOLFIRINOX to
Remove the Bolus Dose of 5-FU**

CSPC argues that a POSA would have been motivated to remove the 400 mg/m² bolus dose of 5-FU. *See* Paper 1 at 43. In support of this argument, CSPC

relies on Mahaseth, a reference that CSPC characterizes as “not discussed during prosecution.” *Id.* CSPC’s arguments in this regard fail.

The Patent Office has already considered Mahaseth and its alleged teachings. CSPC alleges that Mahaseth teaches a modified FOLFIRINOX regimen that does not include the bolus dose of 5-FU. *See* Paper 1 at 43. The Examiner considered Mahaseth, and its alleged teachings, during prosecution. Ex. 2003 (August 26, 2021 IDS) at 28; Ex. 2002 (July 8, 2019 IDS) at 16. The Examiner also considered Marsh, which reflects the same alleged teaching. *See* Ex. 2003 (August 26, 2021 IDS) at 26 (citing Marsh); Ex. 2004 (Marsh) at 3 (Table 2 listing known modifications to FOLFIRINOX that included removal of the 5-FU bolus, including the study described in Mahaseth). In fact, “Drop FU bolus” is a modification identified for four of the six studies listed in Table 2 of Marsh. *Id.* Thus, the Patent Office has already considered patentability of the claimed methods in view of this modification to FOLFIRINOX.

2. CSPC Identifies No Material Error in the Patent Office’s Determination of Patentability

As discussed, CSPC relies on, as its lead references, the same two references that were the most extensively discussed during prosecution of the ’552 patent. CSPC moreover argues obviousness based on the same modifications to the FOLFIRINOX regimen that the Patent Office has already considered. Thus, CSPC presents the same or substantially the same arguments and/or art as those

previously presented to the Patent Office. *See Advanced Bionics*, IPR2019-01469, Paper 6 at 8-9. And, as also discussed, the Patent Office found the '552 patent claims non-obvious in spite of those arguments.

The next step is to determine “whether the petitioner has demonstrated that the Office erred in a manner material to the patentability of the challenged claims.” *Advanced Bionics*, IPR2019-01469, Paper 6 at 8. “If reasonable minds can disagree regarding the purported treatment of the art or arguments, it cannot be said that the Office erred in a manner material to patentability.” *Id.* at 9. Moreover, a petitioner “must provide an analysis even when the asserted prior art is on an IDS, but the Examiner did not apply the reference.” *Ecto World, LLC v. RAI Strategic Holdings, Inc.*, IPR2024-01280, Paper 13 at 5 (PTAB May 19, 2025) (precedential).

CSPC alleges several errors committed by the Patent Office, namely: (1) that Ipsen “led the Office into error” by arguing that a POSA would not have been motivated to combine the teachings of first-line therapy with that of second-line therapy; and (2) that the '552 patent applicant failed to properly identify unexpected results of the claimed combination therapy. Paper 1 at 32-35. For reasons discussed below, each of these arguments falls far short of establishing error “in a manner material to patentability.” *See Advanced Bionics*, IPR2019-01469, Paper 6 at 8-9. Denial under 35 U.S.C. § 325(d) is warranted.

(a) The Patent Office Was Not “Misled” by Arguments Regarding the Teachings of First-Line Versus Second-Line Therapy

CSPC argues that Ipsen “led the Office into error by arguing that there was no motivation to combine Conroy’s first-line FOLFIRINOX regimen with the liposomal irinotecan pancreatic treatment methods of Bayever.” Paper 1 at 32. As support, CSPC cites the ’552 patent applicant’s arguments in the subsection titled, “No motivation to combine the references,” in remarks submitted on February 25, 2022. *Id.* (citing Ex. 1119 at 145-148).

CSPC’s citation is misleading insofar as its cited subsection contains several arguments, not limited to those relating to combining the teachings of first- and second-line therapies. *See* Ex. 1119 at 145-48. The argument that CSPC alleges to have “[mis]led” the Patent Office appears in a single paragraph of the cited subsection. Ex. 1119 at 146. In that paragraph, the ’552 patent applicant argues that “there is no basis for combining Conroy and Bayever because there is no basis for combining teachings regarding second-line therapy with teachings regarding first-line therapy.” *Id.* The remainder of that subsection addresses the Patent Office’s argument, based on Melis, that oxaliplatin (and its dosage) is a result-effective variable. *See id.* at 146-48. As discussed *supra*, this is one of the arguments that the ’552 patent applicant overcame (and that CSPC reargues in its

petition), separate from the argument that CSPC argues “[mis]led” the Patent Office.

CSPC’s argument mischaracterizes the ’552 patent applicant’s statements to the Patent Office. The ’552 patent applicant did not argue, as CSPC and Dr. Ratain state, “that Bayever was limited to treating pancreatic cancer only as a second-line therapy.” Ex. 1002 at ¶ 130; *see also* Paper 1 at 32. Rather, the ’552 patent applicant represented that Bayever covers, but is not limited to, a second-line therapy regimen. Ex. 1098 at 206 (“This liposomal irinotecan, 5-FU, LV regimen is described in Bayever.”); Ex. 1119 at 146 (“Bayever covers the liposomal irinotecan, 5-FU, LV regimen currently approved for ONIVYDE® . . . as a second-line therapy for metastatic pancreatic cancer.”). Thus, CSPC misrepresents the statements alleged to have “led the Office into error.”

Given the extent to which the Patent Office cited and discussed Bayever during prosecution, it strains credulity to argue that the Patent Office was somehow “led” into an erroneous understanding of its contents. Besides Conroy, Bayever was the most frequently cited and extensively discussed reference during prosecution. The Patent Office cited and discussed the disclosure of Bayever in every rejection leading up to resolution of the issue of obviousness in Ipsen’s favor. Under these circumstances, the Patent Office is presumed to have read and understood the contents of Bayever, including the sections that CSPC’s expert, Dr.

Ratain, cites¹ as disclosing first-line treatment. *See Johnson & Johnson Surgical Vision, Inc. v. Alcon Inc.*, IPR2021-00898, Paper 17 at 34-35 (PTAB Nov. 9, 2021) (rejecting an argument that examiners had failed to “fully consider” the disclosure of prior art repeatedly cited and extensively discussed during prosecution); *cf.* *BlephEx, LLC v. Myco Indus., Inc.*, 24 F.4th 1391, 1402 (Fed. Cir. 2022) (affirming district court determination of likelihood of success in defeating a validity challenge that was based on prior art that was before the Patent Office, on the rationale that “the patent examiner is presumed to have considered it”); *Stone Basket Innovations, LLC v. Cook Med. LLC*, 892 F.3d 1175, 1179–80 (Fed. Cir. 2018) (in affirming denial of a motion under 35 U.S.C. § 285, explaining that “where a party only relies on prior art considered by an examiner in its invalidity contentions, that party has the burden to overcome the deference that is due to a qualified government agency presumed to have properly done its job, which includes one or more examiners who are assumed to have some expertise in interpreting the references and whose duty it is to issue only valid patents.” (internal quotations and alterations omitted)). Similarly here, the examiner should be presumed to have read Bayever in its entirety.

¹ See Ex. 1002 at ¶¶ 131-37.

Nevertheless, the prosecution history contradicts CSPC's argument that arguments related to the teachings of first-line versus second-line therapy resulted in any error material to patentability. The '552 patent applicant presented this argument in remarks that did not result in allowance of the claims. In its February 25, 2021 remarks, the '552 patent applicant "provide[d] additional background that may help distinguish the claimed methods from the cited disclosures" of Conroy and Bayever. Ex. 1098 at 206. Specifically, the '552 patent applicant distinguished second-line therapy (as covered by Bayever) from Conroy's disclosure of first-line therapy. *Id.* The Patent Office maintained its obviousness rejection notwithstanding this distinction. *See* Ex. 1119 at 13-15 (finding the '552 patent applicant's arguments "not persuasive"). Thus, even assuming that the '552 patent applicant somehow "[mis]led" the Patent Office regarding the teachings of Bayever (it did not), it was not material to a determination of patentability.

CSPC's reliance on Ko and Saif does not reveal any error made by the Patent Office. As discussed *supra*, Ko was before the Patent Office during prosecution, and both references describe clinical studies that were before the Patent Office during prosecution. They present no new information or basis for concluding that the Patent Office erred in allowing the '552 patent claims.

**(b) The '552 Patent Applicant Properly Identified
Unexpected Results of the Claimed Combination
Therapy**

CSPC also argues, in an attempt to evade discretionary denial, that the evidence of unexpected results submitted by the '552 patent applicant was “defective.” *See* Paper 1 at 33-35. CSPC’s critiques 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. *Id.* Neither argument has merit.

Again, CSPC mischaracterizes the '552 patent applicant’s statements to the Patent Office. The '552 patent applicant submitted that the claimed methods—which comprises dose reduction of two drugs and a dose of liposomal irinotecan that is a fraction of the irinotecan contained in FOLFIRINOX—unexpectedly showed “tolerability *and* efficacy.” 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)). The '552 patent applicant did not—as CSPC misleadingly suggests—simply cite superior efficacy over FOLFIRINOX as a basis for unexpected results.

The Patent Office is presumably aware of the alleged “inherent limitations” that CSPC cites with respect to the ’552 patent applicant’s submitted references. *See* Paper 1 at 34-35. As CSPC acknowledges, the Wainberg article states the “limitations” upon which CSPC relies and cautions against cross-trial comparisons. Paper 1 at 34 (citing Ex. 1019 at 8). The Wainberg references are moreover listed on the face of the ’552 patent. *See* Ex. 1001 at 16 (identifying Ex. 1018); *id.* at 19 (identifying Ex. 1019). The Patent Office is presumed to have read the Wainberg references and drawn its own conclusions. *See, e.g., Johnson & Johnson*, IPR2021-00898, Paper 17 at 34-35 (denying institution, in part on the rationale that the examiner is presumed to have read references before the Patent Office during prosecution); *cf. BlephEx*, 24 F.4th at 1402 (“[T]he patent examiner is presumed to have considered” references “cited on the face of the [] patent.”).

CSPC attempts to negate the ’552 patent applicant’s evidence of unexpected results on the same basis that it criticizes that evidence. Namely, CSPC cites references that purport to draw conclusions of comparative efficacy based on cross-trial comparisons. For example, Nichetti (Ex. 1010) purports to “derive survival, response and toxic effects data from [three separate] phase 3 clinical trials.” Ex. 1010 (Nichetti) at 1. Nichetti acknowledges that its meta-analysis is subject to numerous limitations. *See id.* at 10 (section titled, “Limitations”). Nevala-Plagemann (Ex. 1011) is an opinion piece that questions conclusions drawn

from clinical trials of NALIRIFOX and FOLFIRINOX. *See* Ex. 1011 (Nevala-Plagemann). To the extent that CSPC critiques Wainberg as impermissibly comparing efficacy outcomes across different clinical trials, CSPC does the same.

The '552 patent applicant's evidence of unexpected results shows that NALIRIFOX (the claimed treatment regimen) resulted in improvement in overall survival (OS) and progression-free survival (PFS). *See* Ex. 1018 (Wainberg 2020), Ex. 1019 (Wainberg 2021). Evidence of unexpected results may support a finding of non-obviousness. *See Millennium Pharm., Inc. v. Sandoz Inc.*, 862 F.3d 1356, 1368 (Fed. Cir. 2017) (unexpected results are among objective indicia that enable "the court to avert the trap of hindsight." (citation omitted)). The '552 patent applicant's evidence of unexpected results submitted by the '552 patent applicant during prosecution properly supports non-obviousness of the claimed treatment methods.

CSPC cites the Phase III trial of NALIRIFOX as showing no improvement in these outcomes over FOLFIRINOX but ignores the difference in comparator arms between the relevant Phase III studies. *See* Paper 1 at 34-35, 51-52. The comparator arm for the Phase III study of NALIRIFOX ("NAPOLI 3") was gemcitabine + nab-paclitaxel ("GnP"). *See* Ex. 1010 at 6, Table Summary of Clinical Trial Characteristics. The comparator arm for the Phase III study of

FOLFIRINOX (“ACCORD 11,” as reported in Conroy) was gemcitabine. *Id.* GnP had previously been shown to improve survival over gemcitabine. *See* Ex. 2005 (Mohammed) at 2 (showing an improvement of 8.5 months, over 6.7 months). The fact that NALIRIFOX demonstrated an improvement over GnP (a comparator arm proven to be superior to the comparator arm referred to in Conroy) supports the clinical superiority of NALIRIFOX over FOLFIRINOX. Indeed, more recent publications indicate that a modified FOLFIRINOX regimen has failed to demonstrate superiority to GnP. *See, e.g.,* Ex. 2033 (Skorupan) at 3 (““NALIRIFOX led to better outcomes than GnP, but [a modified FOLFIRINOX regimen] failed to do so.”). This contradicts CSPC’s assertion that the claimed NALIRIFOX regimen is “identical” to that of FOLFIRINOX.

To the extent that CSPC argues that the Patent Office erred in its consideration of “post-filing” evidence to support patentability, that argument fails as a matter of law. CSPC argues against discretionary denial, in part on the Patent Office’s reliance on “post-filing” evidence of unexpected results. Paper 1 at 33-34. That evidence of unexpected results is “post-filing” does not render it immaterial to patentability. Rather, and 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*

Pharmaceutical Co., Inc. v. Teva Pharmaceuticals USA, Inc., 367 F.3d 1381, 1385 (Fed. Cir. 2004) (“Evidence developed after the patent grant is not excluded from consideration, for understanding 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.

Finally, CSPC attempts to find fault with the Patent Office’s patentability determination by manufacturing a claim-construction dispute. Specifically, CSPC argues that the evidence of unexpected results presented to the Patent Office should be discounted, because “a proper claim construction of ‘method of treatment’ does not require clinical efficacy in a human patient.” Paper 1 at 35. In other words, CSPC suggests that the Patent Office relied on an erroneous interpretation of the claims, which required the efficacy reflected in the ’552 patent applicant’s evidence of unexpected results.

CSPC cites no authority for the proposition that an unexpected result is necessarily a claim limitation. Regardless, the ’552 patent claims read in light of the specification cover efficacious treatments. The ’552 patent specification describes that certain doses are as effective in the claimed treatment methods, and the ’552 patent claims recite specific doses. *See, e.g.*, Ex. 1001 (’552 patent) 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), and 12:53-58 (regarding an “effective” dose of oxaliplatin). Thus, the claims cover effective methods of treatment.

B. CSPC’s Flawed Obviousness Arguments Favor Denial

Among the factors the Board may consider in its decision to exercise discretionary denial are: (1) “[t]he strength of the unpatentability challenge;” and (2) “[t]he extent of the petition’s reliance on expert testimony.” March 26, 2025 Memorandum at 2-3. As discussed *supra*, the Patent Office has already found the claims patentable over the same or substantially the same arguments and lead references that CSPC presents. And, as discussed below, CSPC and its expert Dr. Ratain present obviousness arguments that suffer from defects that undermine the strength of CSPC’s challenge and further favor denial of its petition.

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

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. In doing so, CSPC and Dr. Ratain myopically ignore the existence of other treatment options and related considerations that undermine 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 showing therapies for management of pancreatic cancer). 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.

Even assuming that a POSA would have been motivated as CSPC suggests, the low success rate of new treatments for metastatic pancreatic cancer undermines any reasonable expectation of success. This case is analogous to *OSI v. Apotex*, in which the Federal Circuit reversed a PTAB determination of obviousness. *See OSI Pharms., LLC v. Apotex Inc.*, 939 F.3d 1375, 1385 (Fed. Cir. 2019). In doing so, the Federal Circuit relied on evidence of particularly low success rates in the drug development pathway (from early stage trials to FDA approval) for new treatments in oncology, in particular non-small cell lung cancer (NSCLC). *Id.*

Indeed, the success rate for oncology drugs remains the lowest of all therapeutic areas. 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 15 (reporting NSCLC as 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 (13.3%, 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.

Notably, the only data that CSPC cites as support for any reasonable expectation of success is preclinical data regarding liposomal irinotecan (in Bayever) and the initiation of an open-label, Phase II study of the claimed regimen (Dean). See Paper 1 at 8, 61. Critically, CSPC cites no data reflective of the claimed regimen, including all four chemotherapy drugs combined in the recited amounts. The preclinical data in Bayever cannot alone support a reasonable expectation of success for the claimed regimen. See, e.g., Ex. 2007 (Valsecchi) at

6-8 (discussing negative trials—a biological rationale for further study does not equate to a reasonable expectation of success). And CSPC’s own expert agrees that—even if Dean disclosed any clinical data, which it does not—early-phase oncology clinical trial results are not predictive of success in terms of FDA approval. *See, e.g.*, Ex. 2010 (Ratain 2005) at 1 (“[I]t is 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.)” (emphasis added)). For at least these reasons, CSPC is unlikely to prevail in its obviousness challenge.

2. CSPC’s and Dr. Ratain’s Obviousness Argument Is Inconsistent with the ’552 Patent Claims

As discussed, the FOLFIRINOX regimen of Conroy (Ex. 1003) is the basis for CSPC and Dr. Ratain’s obviousness challenge. And, as discussed, CSPC and Dr. Ratain argue that a POSA would have been motivated to modify FOLFIRINOX by, among other modifications, specifically reducing the dose of oxaliplatin from 85 mg/m² to 60 mg/m². As discussed below, Dr. Ratain relies on Conroy as the basis for this alleged motivation but fails to account for a discrepancy between Conroy’s disclosure and the ’552 patent’s claimed dosage of oxaliplatin.

Dr. Ratain relies on Conroy’s disclosure of a “median relative dose intensity” for oxaliplatin as the basis for his opinion. *See, e.g.*, Ex. 1002 at ¶ 241. Conroy states that, of the patients described in the study, “[t]he median relative dose intensities of fluorouracil, irinotecan, oxaliplatin, and gemcitabine were 82%, 81%, 78%, and 100%, respectively.” Ex. 1003 (Conroy) at 4. Dr. Ratain opines that “[a] POSA would understand that the median relative dose intensity is a way to describe what percentage of the dose identified in the formal regimen was given to a typical patient.” Ex. 1002 at ¶ 97; *see also id.* at ¶ 241 (“Conroy disclosed that a median relative dose intensity of oxaliplatin of 78% of the 85 mg/m² oxaliplatin was used in the study.”). Based on this disclosure, Dr. Ratain (and CSPC) argue that a POSA would have been motivated to reduce the oxaliplatin dose of FOLFIRINOX from 85 mg/m² to 60 mg/m². *See* Ex. 1002 at ¶ 105; Paper 1 at 16.

But Dr. Ratain and CSPC ignore that the disclosure of Conroy, if understood in accordance with Dr. Ratain’s opinion, does not lead to the claimed dose. Specifically, 78% of Conroy’s 85 mg/m² oxaliplatin dose is *not* the claimed 60 mg/m² dose (instead, it is 66.3 mg/m²). Dr. Ratain does not even attempt to reconcile this discrepancy, nor does CSPC. Nor do CSPC or Dr. Ratain even argue that Conroy teaches—as claimed—a reduced dose of oxaliplatin *ab initio*. These critical failures undermine CSPC’s obviousness argument and further support denial of its petition.

C. Ipsen's Investment in and Contribution to Patient Care Favors Denial

In accordance with the March 26, 2025 Memorandum, an additional factor that informs the Board's decision of discretionary denial includes the "[s]ettled expectations of the parties." March 26, 2025 Memorandum at 2-3. As discussed below, this factor also favors denial of CSPC's petition.

Ipsen has a settled expectation with regard to its investment and effort bringing a novel treatment option to patients with metastatic pancreatic cancer. As discussed *supra*, pancreatic cancer is among the leading causes of cancer-related deaths, and treatment options remain limited. Over the past several decades, improvements have been made, often by increasing survival time by modest increments. Prognoses for patients diagnosed with metastatic pancreatic cancer remains grim. Patients have an interest in new therapies, which are incentivized by innovators being able to protect their inventions.

Despite low likelihood of success (discussed *supra*), Ipsen and its predecessor Merrimack Pharmaceuticals spent many years and substantial resources investing in developing a new treatment option. Clinical research and drug development is time-consuming and expensive, and even more so in the research and development of new oncology drugs. Clinical trials for new treatments in oncology are among the most expensive of all therapeutic areas. *See, e.g.,* Ex. 2011 (ERG 2014) at 29-30 (ranking oncology as the third-most expensive

therapeutic area, with an average total cost of approximately \$78 million per clinical trial).

Clinical trials for new oncology drugs are not only particularly costly but also present challenges that are not faced in other therapeutic areas. Unlike clinical trials in other diseases, clinical trials for oncology drugs are subject to oversight by multiple federal agencies, which introduces complexity in compliance issues. *See* Ex. 2011 (ERG 2014) at 46 (“In particular, oncology research may be subject to the requirements and guidance of not only FDA, but also the Office for Human Research Protections (OHRP), the National Institutes of Health (NIH), and the Office for Civil Rights (OCR), depending on the study.”); *see also* Ex. 2012 (Govindan) at 1 (“[I]t’s worth noting that oncology drugs are attacking disease entities of enormous complexity and FDA standards for approval with good reason are increasingly more demanding.”). Another challenge faced by clinical trials in oncology is low rates of patient enrollment, which often result in high rates of premature closure due to insufficient patient accrual. *See, e.g.,* Ex. 2013 (Schroen) at 1. In spite of these challenges, Ipsen undertook the time, effort, and expense to bring Onivyde[®] to patients and physicians and has an interest in, and expectation of, protecting its invention.

IV. CONCLUSION

For the reasons set forth herein, the Board should deny CSPC's petition. CSPC argues obviousness based on the same two lead references over which the Patent Office has already found the '552 patent claims non-obvious. To the extent that CSPC purports to identify "new" arguments, they are predicated on references that were already before the Patent Office and/or cumulative of references explicitly discussed by the Patent Office during prosecution. Moreover, CSPC fails to establish material error in the Patent Office's determination of patentability. In addition, CSPC's obviousness challenge suffers from weaknesses, and the investments and contributions made by Ipsen merit consideration. Taken together, these factors justify the Board's exercise of discretionary denial.

Date: May 23, 2025

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

The undersigned hereby certifies that, according to the word-processing system used to prepare the foregoing document, this document has 7,924 words and thus complies with the applicable word limit.

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

The undersigned hereby certifies that on 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):

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